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SURGERY

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Original Communications

Society for Vascular Surgery

DISEASES OF THE SUPERIOR VENA CAVAL SYSTEM WITH SPECIAL CONSIDERATION OF PATHOLOGY AND DIAGNOSIS

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WASHINGTON, D. C.

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FOR many years we have been particularly interested in diseases of the peripheral veins. Certain members of the Georgetown Staff have collaborated in a prolonged investigation of these diseases at the Gallinger Hospital. This is the general hospital for the District of Columbia and has a capacity of over 1,400 beds. In this communication we wish to present our experiences in this hospital with diseases of the superior vena caval system.

There are several reasons for this study:

1. To demonstrate the infrequency of diseases affecting the superior vena caval system.
2. To discuss the value of certain tests in the diagnosis and prognosis of these diseases.
3. To illustrate the specific syndromes produced by occlusion of the main segments of this system.
4. To present an analysis of the causes of obstruction of the various components of the superior vena caval system.
5. To present an unusual group of cases of septic thrombophlebitis of the brachial veins in heroin addicts.

The small number of cases we have encountered indicates that diseases of the superior vena caval system are uncommon. In fact, this system is so infrequently involved that when some part is affected it is likely to provide a diagnostic problem. However, by applying certain tests, not only can the diagnosis of venous obstruction be confirmed but the point of obstruction and its cause can usually be revealed.

Presented at the fifth annual meeting of the Society for Vascular Surgery, Atlantic City, N. J., June 10, 1951.

In general the four cardinal symptoms of acute obstruction of a major vein are venous engorgement, edema, cyanosis, and pain in that portion which is drained by the occluded vein. The intensity of these symptoms depends upon the suddeness of the occlusion and the availability of collateral pathways. It is through the dilatation and extension of the collateral veins that the circulation is restored.[1, 2] In obstructive diseases of the superior vena cava or any of its main tributaries the superficial veins dilate quickly and a distinctive pattern forms one of the important signs in the diagnosis and the localization of the site of obstruction. The diagnosis can be confirmed by differential venous pressure determinations and appropriate venograms.

The superior vena caval system can be explored relatively easily by means of phlebography.[3] The system is short and the contrasting intrathoracic densities make this method of study more reliable than when it is applied to the veins of the inferior system. The injection of the opaque material can be made into any of the available tributaries or by direct catheterization through the external jugular veins.

Phlebograms are of value in several ways. They reveal the size, number, and distribution of the collateral channels.[4] The actual site of the obstruction can be shown by selective phlebograms. They may be diagnostic of the cause of the venous obstruction.

The point of occlusion of the axillary or subclavian veins and the collateral vessels can be demonstrated by injecting 10 c.c. to 15 c.c. of Diodrast into any of the veins of the forearm or hand. If the injection is made directly into the cephalic vein the material may be dispersed through the collaterals and may fail to enter the axillary vein. In obstruction of the superior vena cava and/or innominate veins a similar injection would show only the superficial collaterals. The venous pressure is so great in the intrathoracic veins that as the opaque material approaches the shoulder region it may all be diverted through the collaterals. To visualize clearly the innominate veins or superior vena cava larger doses of 70 per cent Diodrast must be used. It may be injected under force and at a rapid rate into an arm vein, or by catheter into the external jugular vein.

Phlebograms may be of value in determining the causes of the obstruction of the innominate veins or the superior vena cava. We have seen cases of right upper chest and mediastinal masses in which the differential diagnosis clinically rested between aneurysm with atelectasis and carcinoma with atelectasis. The usual roentgenographic studies did not settle the problem. Right external jugular vein phlebography demonstrated complete obstruction and dilatation of the superior vena cava in situ. This established the diagnosis of malignancy, because aneurysms of the arch and ascending aorta produce obstruction of the superior vena cava by displacement and compression.

The measurement of the venous pressure is the simplest way to confirm the presence of obstruction of the superior vena cava or its tributaries. The technique we employ in recording the intravenous pressure has been adequately described in previous communications.[5, 6]

In the normal subject, at rest and in a supine position, and with normal respiration, the antecubital venous pressure ranges from 50 to 150 mm. of normal saline solution. On inspiration the pressure falls slightly, and on expiration it is slightly elevated. The pressure in the femoral veins has the same normal range but the response to respiration is just the opposite from that observed in the upper extremities. The comparison between the pressure recordings in the upper extremities and that from the veins of the lower extremities is deisgnated as the differential pressure.

The discovery of venous hypertension in the upper extremities and normal venous pressure in the femoral veins etsablishes the diagnosis of obstruction of the superior vena cava and/or both innominate veins. There may be some variations in the degree of elevation of the pressure in the two arms because of the difference in the amount of constriction of the innominate veins. This is often found when an aortic aneurysm is the cause of obstruction.

The demonstration of a high venous pressure in but one upper extremity and normal venous pressure in the other and in the femoral veins confirms the diagnosis of obstruction of the axillary and subclavian veins and/or the innominate vein on that side. The presence of distention of the internal jugular veins and/or venous hypertension of those veins distinguishes innominate obstruction from axillary and subclavian vein occlusion.

The value of the venous pressure studies has been enhanced by recording the pressure during activity of the involved limb. We have previously described an "exercise test"[7] which is easily applied to the upper extremities. Muscular activity increases the rate and volume of blood flow through an extremity. If the vascular bed is normal, the increased blood flow is accommodated by dilatation of the vessels. As much blood can leave as enters and the venous pressure is only very slightly affected. However, if there is any degree of obstruction to the venous outlet, the flow will be retarded. The veins will become congested and the intravenous pressure will rise. On cessation of the activity there will be a slow decline in the pressure until it again reaches its initial level. Such a curve is pathognomonic of venous obstruction. In congestive heart failure, where the initial systemic venous pressure is abnormally elevated, the pressure response to muscular activity is the same as in the normal subject. This so-called exercise test has proved to be quite valuable in ascertaining the presence of varying degrees of obstruction of the veins of the superior vena caval system. Furthermore, the amount of the increase in pressure during exercise, and the rate of the decline when the exercise is concluded give considerable information on the efficiency of the collateral circulation.

The value of phlebography and the venous pressure determinations will be borne out by the following report.

During the fifteen-year period, we have had the opportunity to study 137 cases of diseases involving the superior vena cava or one or more of its major tributaries. We have not included any patients with derangements of the

venous circulation of the arm following radical amputation of the breasts, nor any with minor chemical thrombosis from intravenous medication. The distribution of cases is shown in Table I.

TABLE I. DISEASE OF THE SUPERIOR VENA CAVAL SYSTEM

SEGMENT INVOLVED	NUMBER OF CASES
Superior vena caval obstruction	50
Innominate vein obstruction	11
Thrombosis, axillary and subclavian veins	58
Septic thrombophlebitis	
Jugular veins	4
Brachial veins (heroin addicts)	14
Total	137

Each group will be discussed separately in order to emphasize the corresponding clinical syndrome.

OBSTRUCTION OF THE SUPERIOR VENA CAVA

The clinical syndrome produced by obstruction of the superior vena cava has long been recognized.[8-10] The acute stage is characterized by engorgement of all of the venous radicles of the superior vena caval system followed by rapid development of edema of the same region. Local cyanosis may be a striking sign. The venous pressure differential reveals a very high pressure in the arm veins and a normal pressure in the femoral veins. All other symptoms such as dyspnea, cough, chest pain, etc., are mainly the result of the causative factor and not due primarily to the obstruction of the vena cava. Apparently the heart suffers little and the pulmonary circulation remains intact. The acute symptoms usually subside within one to three weeks and then the picture resembles that produced by a gradual obstruction or incomplete occlusion. In this group there may be no subjective symptoms. The essential findings are those of venous hypertension of the superior vena caval system and the appearance of the superficial venous collaterals. While this venous pattern is characteristic, it is not present in all cases of obstruction of the superior vena cava. It depends upon the location of the obstruction. If it occurs above the point where the azygos enters, the azygos takes over the function of the superior vena cava in returning blood from the upper part of the body to the right heart. In such cases the deep veins form the main collateral channels and the superficial network may be little affected. When obstruction occurs below the azygos, all blood returns to the heart via the inferior vena cava, and extensive collaterals are seen on the thorax and abdomen. These vessels become the main channels for returning the blood to the heart via the inferior vena caval system. Therefore, when they are constricted by placing a tourniquet around the chest wall, the intravenous pressure manometer rises on inspiration. This, as has already been pointed out, occurs normally when recording the pressure in the inferior vena cava. These tests demonstrate to a degree the efficiency of the deep collaterals and gives confirmatory evidence of the location of the obstruction.

In this present series there were fifty cases of obstruction of the superior vena cava.

TABLE II. OBSTRUCTION OF THE SUPERIOR VENA CAVA

ETIOLOGY	NUMBER OF CASES
Mediastinal adenopathy	22
Aneurysm of aorta	16
Undetermined (mediastinitis?)	12
Total	50

There were twenty-two cases of obstruction from neoplasms. Bronchogenic carcinoma was the most frequent type of neoplasm encountered (Fig. 1). Various forms of lymphomas accounted for most of the other cases.

In sixteen cases the obstructions were caused by aneurysms of the aorta. In some the obstruction was complete while in others the aneurysm had caused only a partial occlusion. The diagnosis of this type of obstruction is usually simple. It is confimed by presence of the aneurysm plus the telltale superficial venous pattern, the differential venous pressure curves, and the characteristic venogram (Fig. 2).

There were twelve cases in which the exact cause of the occlusion could not be ascertained. These have usually been classified as thrombosis from mediastinitis (Fig. 3). Since all of these caess survived, we prefer to classify them as obstruction from undetermined etiology.

OBSTRUCTION OF THE INNOMINATE VEINS

Diseases affecting primarily a single innominate vein are indeed rare. We have had only eleven such cases. In all, the obstruction was secondary to compression by an aneurysm (Fig. 4). In ten cases the left innominate vein was involved, and in only one was the right innominate vein obstructed. The latter was caused by an aneurysm of the right innominate artery. Occlusion of an innominate vein produces a typical superficial venous pattern. The key to diagnosis is the congestion of the veins of the respective upper extremity plus the distention of the veins of the neck on the same side, while the opposite side is normal. The diagnosis is confirmed by differential venous pressure determinations and venograms.

OBSTRUCTION OF THE AXILLARY AND SUBCLAVIAN VEINS

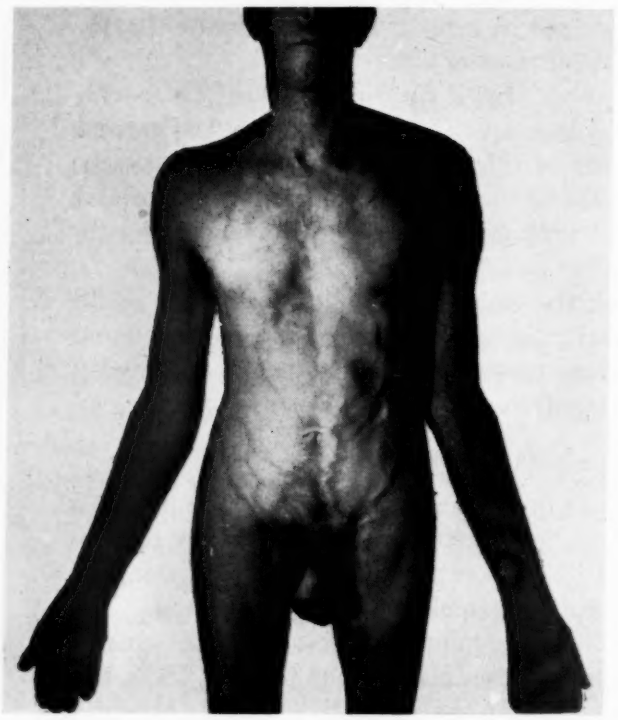
The axillary and subclavian veins were the most frequently involved of all the tributaries of the superior vena cava. We have placed occlusion of the

TABLE III. THROMBOSIS OF AXILLARY AND SUBCLAVIAN VEINS

TYPE	NUMBER OF CASES
Stasis thrombosis (congestive heart failure)	25
Acute thrombosis—effort type	21
Acute thrombophlebitis	2
Thrombosis—secondary to neoplasm	10
Total	58

axillary and subclavian veins in one group because usually both segments are involved together and because the symptoms produced by both are quite similar.

Thrombosis of the axillary and subclavian veins produces a distinctive syndrome which is easily recognized.[11, 12] It seems unnecessary to dwell upon the symptomatology of this condition. Suffice it to say that the acute stage is characterized by pain, swelling, and often cyanosis of the entire upper extremity of the involved side. The arterial circulation remains intact. All of the veins of the limb are engorged and the intravenous pressure reaches a high level. In our cases the initial pressure has ranged between 500 and 1,400 mm.



VENOUS PRESSURE DIFFERENTIAL

PRESSURE	Right Arm	Left Arm	Right Leg
Resting	390	390	40
Inspiration	392	391	41
Expiration	380	380	41
1 min. exercise	420	410	
Band around waist	417		

Fig. 1.—Superior vena caval obstruction by bronchogenic carcinoma. Photograph shows distribution of collateral veins. The venous pressure differential demonstrates venous hypertension of superior vena caval system. The effects on the venous pressure by inspiration, expiration, arm exercise, and the application of band around the waist are shown.

of normal saline solution. The exercise test reveals a further increase in the local venous pressure. A phlebogram will reveal the point of occlusion and the collateral venous pattern.

Thrombosis of the subclavian and axillary veins accounted for 58 cases in this series. In Table III we have listed the cases according to etiology.

There were twenty-five instances of stasis thrombosis in patients with congestive heart failure. It is significant that seventeen out of the twenty-five cases developed pulmonary infarction. There were twenty-one cases of effort thrombosis. There were only two cases of acute thrombophlebitis. In ten the thrombosis was secondary to malignant neoplasms. We have not included any postoperative breast amputation in which the axillary and sub-

Fig. 2.—Obstruction of superior vena cava by aortic aneurysm. Infrared photograph shows distribution of superficial collateral veins. The differential venous pressure is recorded. Venogram shows occlusion of the superior vena cava.

Fig. 3.—Occlusion of superior vena cava by mediastinitis, the acute stage. Note edema beneath eyes and the distention of superficial veins of chest and arms. The venous pressure differential shows marked superior vena caval hypertension. The venogram (retouched) shows the azygos vein replacing the superior vena cava.

clavian veins were secondarily occluded. The acute symptoms of axillary and subclavian vein thrombosis last only a few days. The pain subsides, the cyanosis clears, the edema diminishes, and the venous pressure declines. The typical superficial venous pattern over the shoulder, back, and chest soon becomes evident. The presence of this characteristic pattern may be the only clue to the diagnosis in the postthrombotic stage.

Apparently thrombosed axillary and subclavian veins do not recanalize. The venous return depends upon the collateral veins. They provide adequate channels when the arm is at rest or is mildly active.

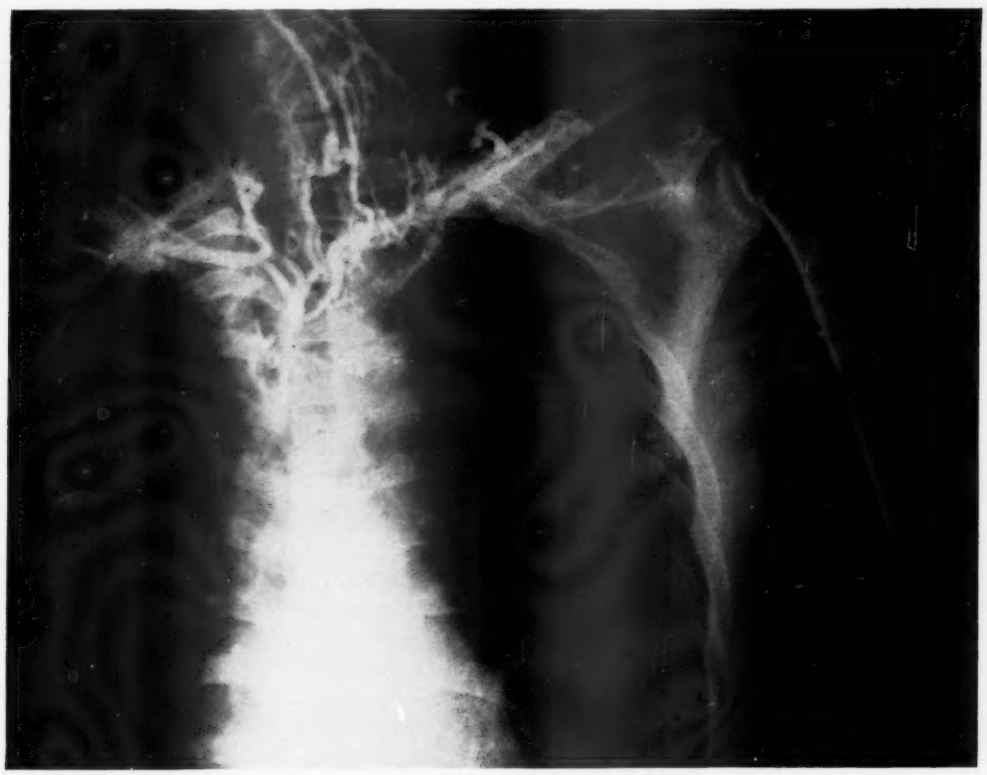


Fig. 4.—Occlusion of the innominate vein by aneurysm. The venogram shows the complete obstruction of the superior vena cava with collateral veins extending into the neck and shoulder regions. The venous pressure differential shows normal venous pressure (118) right arm, venous hypertension left arm (venous pressure, 320).

With greater activity it becomes fatigued. This is often so marked that these patients are seriously handicapped. Matas,[13] in a classical presentation on this subject, emphasized the importance of these residual symptoms.

We have investigated this problem and have found that during exercise the arm veins become congested and there is a rapid rise in the local venous pressure. This pressure also shows a slow decline to normal after the exercise period has been terminated (Fig. 5). These findings clearly demonstrate the inadequacy of the venous return during muscular activity of the extremity. The fatigue and discomfort which occur during rapid use of the involved limb seem to be caused by the retardation of the blood flow.

SEPTIC THROMBOPHLEBITIS

The most interesting group of diseases of the tributaries of the superior vena cava has been that of the eighteen cases of septic thrombophlebitis (Table IV). Fourteen of these occurred in heroin addicts. All were "main liners." The victims were self-inoculated, administering the drug in an arm vein (main line) without sterile precautions. In such cases the presenting picture has been that of a marked local inflammatory reaction of the involved arm and a severe

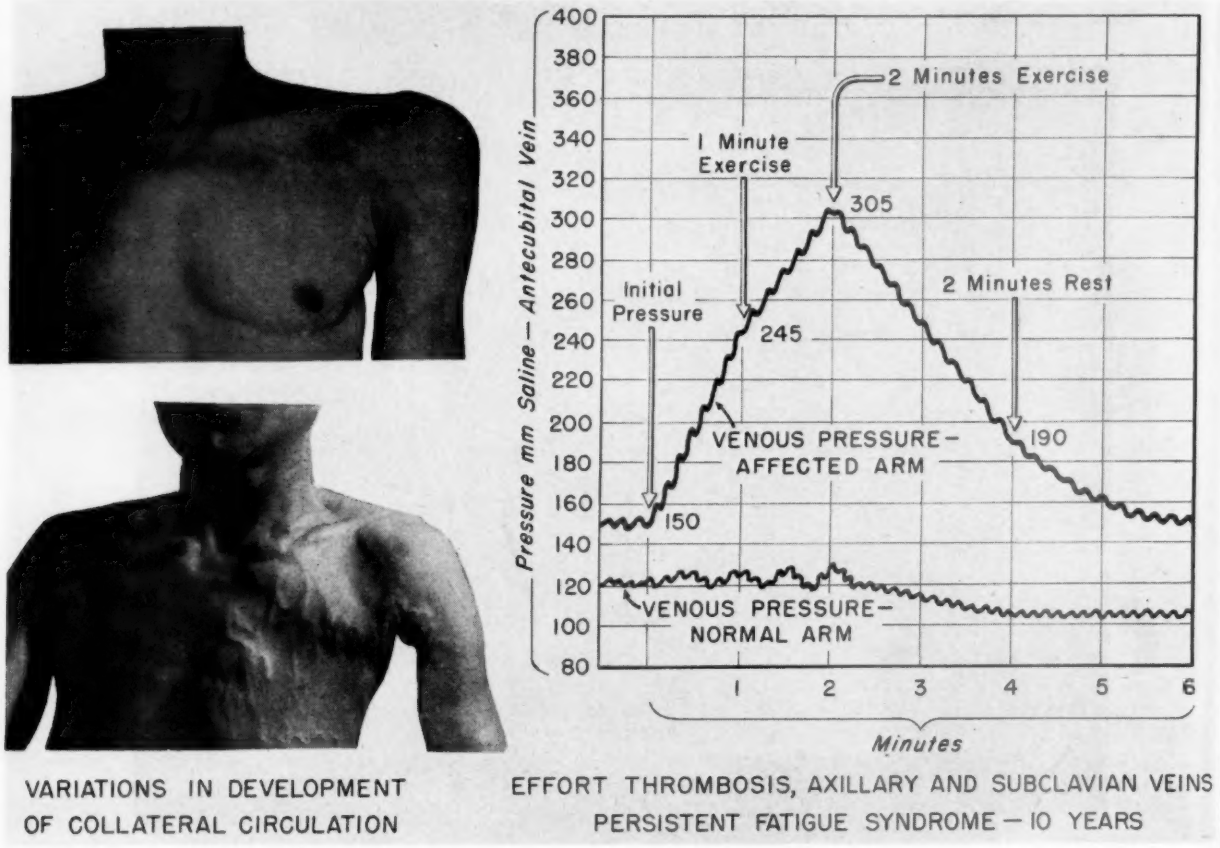


Fig. 5.—Postthrombotic fatigue syndrome-thrombosis of the axillary and subclavian veins. Infrared photographs show variations in development of collateral venous circulation. Note the venous hypertension in the affected arm only during exercise period.

systemic infection. The arm usually exhibited pain, swelling, redness, induration and often abscess formation. In some the thrombosed veins could be clearly outlined. There was also an accompanying axillary adenitis. The chief systemic symptoms were fever, leucocytosis, cough, hemoptysis, and chest pain.

In the four other cases the internal jugular veins were involved.[14] In these the thrombophlebitis resulted from regional neck infections.

A positive blood culture was obtained in twelve of the eighteen cases. Hemolytic Staphylococcus was the predominant organism. In some a hemolytic Streptococcus was found. In one the invading organism was the *Staphylococcus albus.*

Septic pulmonary infarction occurred in fourteen of the eighteen patients.

By the recognition of the septic character of these cases, and the prompt administration of penicillin, all recovered except one case of internal jugular thrombosis. In seven of the patients who were heroin addicts the appropriate vein was ligated proximal to the septic thrombus.

TABLE IV. SEPTIC THROMBOPHLEBITIS

VEINS	NUMBER OF CASES	POSITIVE BLOOD CULTURES	SEPTIC PULMONARY INFARCTION	RECOVERED
Jugular	4	2	4	3
Brachial	14	10	12	14

PULMONARY EMBOLISM IN DISEASES OF THE SUPERIOR VENA CAVAL SYSTEM

Pulmonary embolism is the main catastrophe of diseases of the peripheral veins. The great majority of pulmonary emboli have their origin from the deep veins of the legs. However, certain types of thrombosis of the superior vena caval system produce a very high incidence of pulmonary embolism. In Table V we have listed the cases of venous obstruction in the various portions of the superior vena cava and the incidence of pulmonary embolism.

TABLE V. INCIDENCE OF PULMONARY EMBOLISM IN DISEASES OF THE SUPERIOR VENA CAVAL SYSTEM

SEGMENT INVOLVED	NUMBER OF CASES	PULMONARY EMBOLISM
Superior vena cava	50	0
Innominate veins	11	0
Axillary and subclavian veins		
Effort thrombosis	21	0
Acute thrombophlebitis	2	0
Thrombosis in malignancy	10	0
Stasis thrombosis (cardiac)	25	17
Septic thrombophlebitis		
Jugular vein	4	4
Brachial vein	14	12
Total	137	33

It is readily seen that embolism occurred in only two groups, namely, the group with axillary and subclavian thrombosis in congestive heart failure and the group with septic thrombophlebitis.

SUMMARY

1. Diseases of the superior vena caval system are uncommon. Only 137 cases were encountered at the Gallinger Hospital over a fifteen-year period.

2. The various segments of the system were found to be involved in the following order of frequency: (1) the axillary and subclavian veins, (2) the superior vena cava, (3) the brachial veins, (4) the innominate veins and (5) the jugular veins.

3. From the standpoint of pathology, malignant neoplasms and local infections were equally divided, there being thirty-two cases in each group.

(This includes the questionable mediastinitis cases.) In twenty-seven cases the venous occlusion was caused by compression by aneurysms. Thrombosis resulted from venous stasis in congestive heart failure in twenty-five cases. The remaining twenty-one cases were associated with effort (trauma).

4. Phlebography provides valuable information in determining the point of obstruction and the extent of collateral circulation, and may be important in the differential diagnosis of the cause of the obstruction.

5. Measurement of the venous pressure is the simplest way to confirm the presence of obstruction of the superior vena cava or its tributaries. The exercise test gives additional information particularly on the efficiency of collateral circulation.

6. Main-line heroin addicts, through self-inoculation with pathogenic bacteria, may cause a serious venous infection with frequent septic pulmonary infarction.

7. Pulmonary embolism occurred only in the cases of stasis venous thrombosis and septic thrombophlebitis. The incidence of embolism was almost the same in each of these groups. It occurred in seventeen of the twenty-five cases of stasis thrombosis of the axillary and subclavian veins and in sixteen out of eighteen cases of septic thrombophlebitis.

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THE RESPONSE OF THE CLOTTING EQUILIBRIUM TO POSTOPERATIVE STRESS

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IT SEEMED inevitable that the far-reaching concept of Selye's general adaptation syndrome[1] would be extended to the interpretation of changes occurring in the postoperative state. Nitrogen loss, sodium retention, and potassium excretion have already been connected, at least in part, to the nonspecific stress of surgical trauma.[2] Several authors have followed the convalescence of surgical patients by daily eosinophil counts[3] as a simple expression of stress.

It occurred to us that postoperative changes in the clotting mechanism may also reflect an aspect of the general adaptation syndrome. A simple one-tube clotting time sensitized with heparin has recently been described.[4] Both this test and the eosinophil count can readily be followed daily at the bedside. The prognostic value of such preoperative and postoperative determinations regarding thromboembolic complications was explored in this study.

THE STRESS OF OPERATION

The operative stress is the sum total of several factors, such as the anxiety of the patient, the premedication, the anesthesia, the pre- and postoperative food reduction, and the tissue trauma itself. In a previous communication[4] it was pointed out that the premedication and anesthesia might well account for some of the postoperative changes in the clotting mechanism. The role of liver damage has been suggested by Borgstrom,[5] among others. He observed a fall of the prothrombin levels, maximal on the fourth day, a reaction which did not occur following operations under spinal or local anesthesia.

Previously, the effect of nervous stimuli, especially that of epinephrine, on the heparin tolerance curve has been reported from our clinic.[6] Cannon's observation on shortening of the coagulation time after emotional stress, and stimulation of sensory nerves and splanchnic nerves, all of which cause adrenal discharge,[6] has now been extended in the studies of Hume and Wittenstein, showing that the drop of the eosinophil count in dogs following a standard operation can be eliminated by cord section at the level of C.[7] Also the massive ACTH response which patients exhibit after operation is delayed until a spinal anesthetic wears off.[7] According to the concept of Long and his coworkers, such a procedure only abolishes the autonomic phase of the response to stress, the metabolic one appearing later.[8]

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A major operation usually results in a fall, followed by a rise of eosinophils; eosinophilia may occur on the third or fourth day, during which time the ACTH response is good and the epinephrine response variable.[3d] That there is a postoperative fluctuation in the state of the clotting mechanism has been reported by Borgstrom,[5] Sandrock, and Mahoney,[9] and Halse.[10] The nature of this fluctuation has not been previously established.

METHODS OF STUDY

Patients were admitted at least forty-eight hours before operation. One or two preoperative clotting times were determined simultaneously with eosinophil counts. The sensitized clotting times were observed at the bedside.[4] A clean venous puncture was essential and all "difficult punctures" were discarded. Into a scrupulously clean 10 by 100 mm. test tube, 0.1 c.c. of physiologic saline solution was pipetted, containing 1 gamma of heparin* to which 1 c.c. of venous blood was added. The tube was then stoppered gently, inverted three times, and firmly grasped in the hand for six minutes (thermostatic control), after which it was inverted once every minute to the horizontal level. Disappearance of the fluidity of the blood marked a sharp end point. The normal controls ranged between twelve and sixteen minutes, with a 2 per cent fluctuation of daily controls of young, healthy subjects devoid of stress. In addition, the original heparin tolerance as lately modified by us, has been used for pilot tests before and after operation. Ten milligrams of heparin were injected intravenously, and capillary coagulation times were determined before, and ten minutes after, injection; thus only the rise of the curve and not the fall of the curve were determined. We had 296 controls from a previous study.[11]

For the eosinophil count the method of Randolph[12] was employed. In this method a diluting fluid is used, containing methylene blue and phloxine dissolved in equal parts of propylene glycol and water, which permits the counting of eosinophils in the same counting chamber specimen employed in counting the total leucocytes. The granules of the eosinophil cell stain brilliant red and the limiting membranes of all the white cells remain intact. In addition, Thorn's test[13] which consists of an eosinophil count before, and four hours after, subcutaneous injection of 0.3 mg. of epinephrine, was also frequently used. We have employed this test previously in studying the corticoadrenal response of the hypertensive patient before and after splanchnicectomy.[14]

PREOPERATIVE STUDIES

The epinephrine-eosinopenia was correlated with the response of the sensitized clotting time to epinephrine before operation. Out of a group of twenty-six patients, eight show a fall in eosinophils after injection of 0.3 mg. of epinephrine, together with a lengthening of the clotting time. These are

*In the preliminary report 4 gamma of heparin were employed. However, the decrease in dosage does not impair the sensitivity of the test and shortens the period of observation.

shown in Table I. In a second group of patients, both the eosinophil counts and the clotting times move in the same direction. These are shown in Table II.

TABLE I. RESPONSE OF EOSINOPHILS AND THE SENSITIZED CLOTTING TIME TO 0.3 MG. OF EPINEPHRINE, GROUP 1

CASE	AGE (YEARS)	DIAGNOSIS	EOSINOPHILS IN PER CENT OF PREINJECTION LEVEL	CLOTTING TIME IN PER CENT OF PREINJECTION LEVEL
2	39	Hypertension	–54	+23
4	28	Finger injury	–62	+25
5	55	Hypertension	–44	+25
6	48	Diabetic arteriosclerosis	–	+40
7	54	Fractured knee	–	+20
9	35	Hypertension	–41.6	+ 5.8
15	51	Endarteritis	–36	+33
23	50	Postphlebitic syndrome	–44.2	+ 6
		Average change	–47	+22

TABLE II. RESPONSE OF EOSINOPHILS AND THE SENSITIZED CLOTTING TIME TO 0.3 MG. OF EPINEPHRINE, GROUP 2

CASE	AGE (YEARS)	DIAGNOSIS	EOSINOPHILS IN PER CENT OF PREINJECTION LEVEL	CLOTTING TIME IN PER CENT OF PREINJECTION LEVEL
1	56	Bronchial asthma	–21	–17
8	44	Roentgen-ray dermatitis	–	–26
10	32	Hypertension	–42	–15
11	47	Hypertension	–33	– 6
12	38	Hypertension	–44	0
13	30	Hypertension	–25	–17
14	61	Hypertension	–	–22
16	62	Arteriosclerosis	–45	–50
17	50	Diabetic gangrene	–39	–28
18	15	Megacolon—colostomy	–21	–23
19	47	Hypertension	–58.8	–20
20	50	Leg ulcer, dermatitis	–12.5	–10
21	35	Hypertension	–58	–20
22	41	Diabetes—hypertension	–57.6	0
24	54	Fatigue—hypertension	–72.8	–26
25	34	Leg ulcer, allergy	–32.8	– 7
26	50	Varicose veins	–58.5	–15
		Average change	–41	–18

In only one patient was there a refractory state of both mechanisms. Because of the unusual behavior of this case a brief clinical history is given.

Charles J., a 43-year-old machinist, had thromboangiitis obliterans for several years, which produced a sudden popliteal occlusion on the right side. He was a heavy smoker, showed some myocardial and renal damage, but no evidence of arteriosclerosis. Preoperatively, he showed no drop in eosinophils and no rise in the clotting time on injection of epinephrine. Postoperatively, following a lumbar sympathectomy under spinal anesthesia, he responded with no drop in the eosinophil count, so that an adrenal insufficiency was suspected. However, he made an uneventful recovery. He was an allergic individual, showing sensitivity to tobacco, corn, and wheat. He showed an increased sensitivity to heparin such as we have previously reported.[15]

This observation indicates that allergic individuals cannot be expected to show a normal eosinophil response to operation; also their clotting response may be unusual. Such a refractory state of eosinophils was encountered in another study, where the stress phenomenon in relation to hypertension was being investigated.[14]

There is no evidence to support the assumption that a response to stress mirrored in the eosinophil count would move synchronously in the same direction as the clotting times. In fact, Selye[1b] has made the point that, for instance, tendency to edema, lipid content of adrenals, and weight of the thymus do not traverse the three phases of the adaptation syndrome, namely alarm

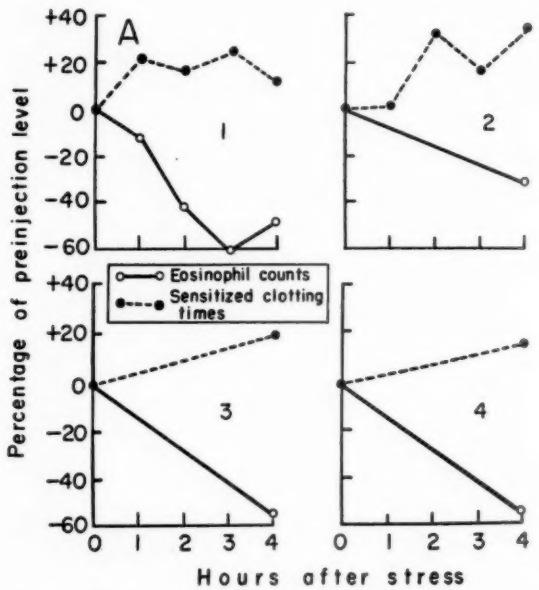

Fig. 1.—Pattern *A*, showing curves of four patients in whom the clotting times rise after epinephrine. The eosinophil response is normal except in Case 2, an ill-nourished individual who had had many weeks of sleepless nights. (*1*) J. H., age 28 years, finger injury; (*2*) E. J., age 51 years, endarteritis obliterans; (*3*) E. K., age 39 years, hypertension; (*4*) B. F., age 55 years, hypertension.

reaction, stage of resistance, and stage of exhaustion at the same time. For this reason it was felt that a few cases should be followed by more frequent determinations to study the time factor in these reactions. Seventeen patients were so studied. Figs. 1 to 4 show various gradations of response; the clotting times are represented by dotted lines, the eosinophil counts by straight lines. Fig. 1 demonstrates the simultaneous curves of eosinophil counts and sensitized clotting times in four patients, all of whom show an eosinophil response to epinephrine with a lengthening of the clotting time. Fig. 2 shows again a good response of the eosinophils to the stress of epinephrine, but a fall of the clotting times with recovery at the end of four hours. In Fig. 3 are shown the curves of five patients with falling clotting times. The eosinophil response is again normal, except for Case 14, a patient with multiple allergic phenomena and a causalgic state. In Fig. 4 a refractory state is shown

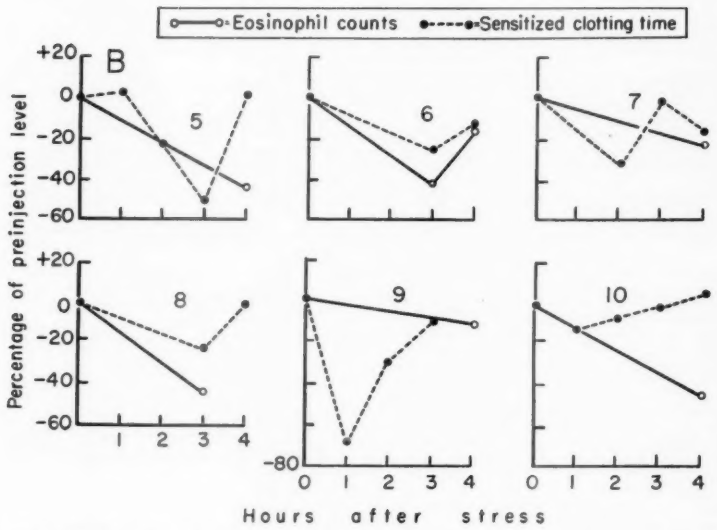

Fig. 2.—Pattern *B*, showing a fall in the sensitized clotting times, but recovery within a four-hour period. (*5*) L. Z., age 62 years, hypertensive cardiovascular disease; (*6*) L. Z., age 56 years, bronchial asthma; (*7*) G. M., age 17 years, megacolon, malnutrition; (*8*) V. S., age 38 years, hypertension; (*9*) F. P., age 50 years, postphlebitic ulcer, dermatitis; (*10*) K. R., age 50 years, postphlebitic varicosities, chronic fatigue. Note the pattern of Case *9*, showing poor response of eosinophils, sharp drop of the clotting time.

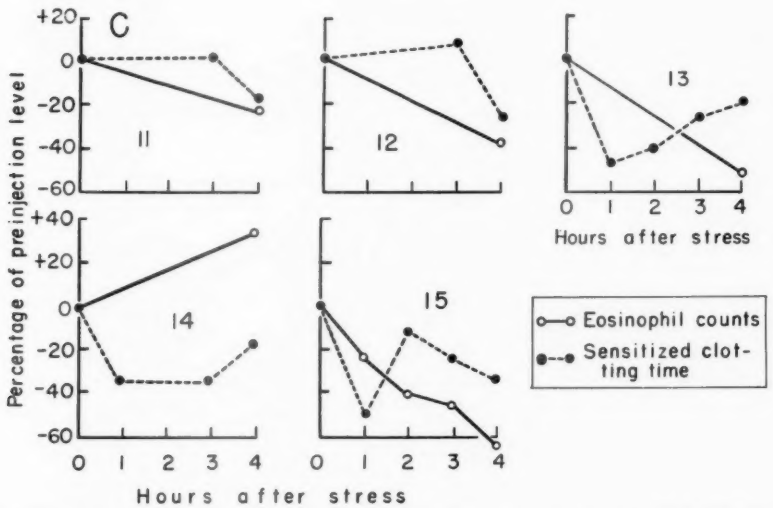

Fig. 3.—Pattern *C*, showing a fall in clotting time, with partial recovery in Case *13*. (*11*) L. R., age 30 years, malignant hypertension; (*12*) L. M., age 50 years, diabetic gangrene, generalized arteriosclerosis; (*13*) E. G., age 47 years, posttoxemic hypertension; (*14*) K. F., age 31 years, minor causalgia, multiple allergies; (*15*) L. S., age 36 years, scleroderma, gangrene following cortisone.

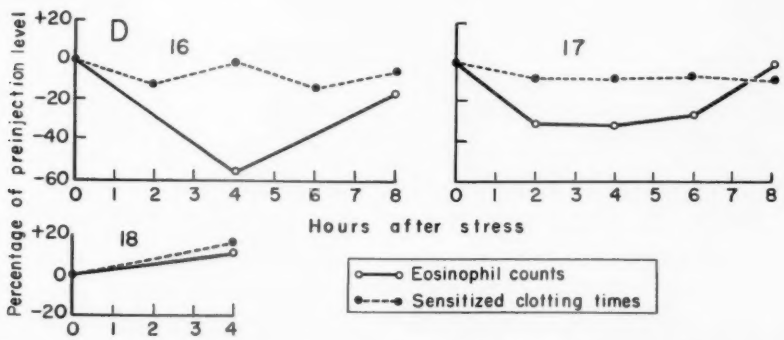

Fig. 4.—Pattern *D*, no response of the clotting mechanism; a refractory state. (*16*) E. S., age 41 years, diabetic hypertension; (*17*) A. F., age 34 years, postphlebitic ulcer, allergy; (*18*) Ch. J., age 43 years, Buerger's disease, allergy.

in three patients, since the clotting time did not respond, while the eosinophils did, at least in Case 16. Since the stimulus is identical and since the adaptation syndrome is functioning as evidenced by the eosinopenia, these patterns must mean differences in the reactivity of the clotting mechanism to stress.

POSTOPERATIVE STUDIES

In an earlier study on postoperative heparin tolerance, curves were shown to become flat in the first few days after operation, with an increasing sensitivity later on; the significance of this finding, although recorded in the graphs, was

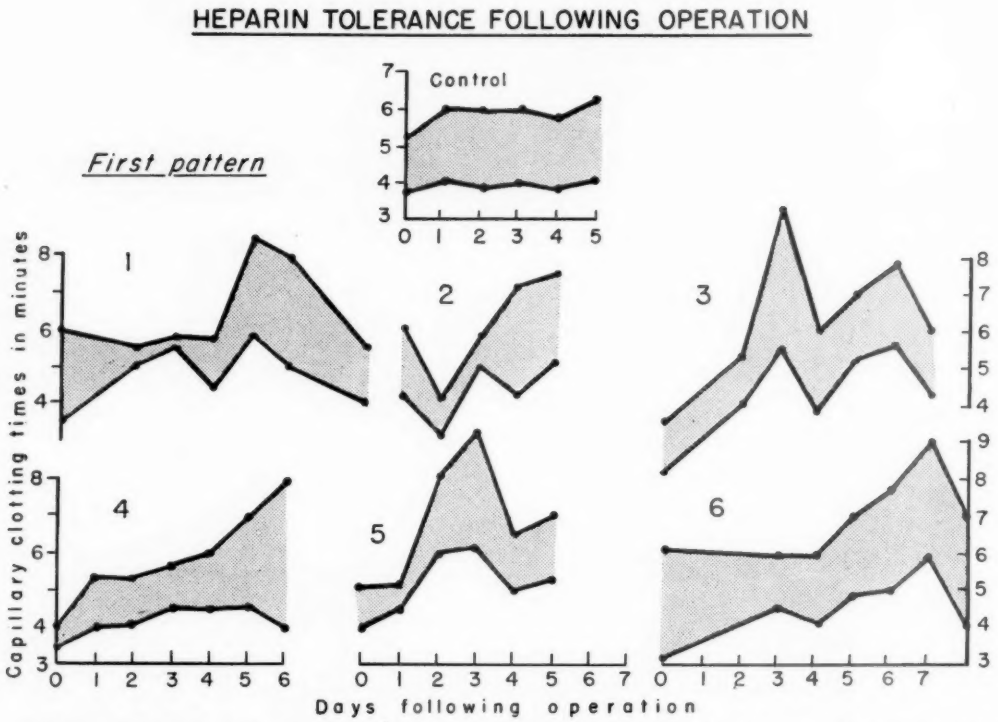

Fig. 5.—Heparin tolerance during the first postoperative week. 10 mg. of heparin were injected intravenously and capillary coagulation times were determined before and ten minutes after the injection of heparin. (*1*) D. N., age 42 years, Buerger's disease, lumbar sympathectomy under spinal anesthesia; (*2*) J. S., age 41 years, Buerger's disease, lumbar sympathectomy under spinal anesthesia; (*3*) M. S., age 43 years, Buerger's disease, lumbar sympathectomy under spinal anesthesia; (*4*) G. Z., age 72 years, generalized arteriosclerosis, thigh amputation under spinal anesthesia; (*5*) W. N., age 44, hypertension, dorsolumbar sympathectomy, intratracheal anesthesia; (*6*) E. H., age 35 years, malignant hypertension, dorsolumbar sympathectomy, intratracheal anesthesia. The control curve is an average of six individual determinations made on patients on whom no operation was performed. Lower dot represents the pre-injection level, upper dot the postinjection level, of capillary coagulation times.

missed.[15] In order to re-examine this phenomenon a few modified heparin tolerance curves[11] were determined as frequently as possible during the first postoperative week. Fig. 5 shows six such curves in which first a decreased, later an increased, heparin response is shown, the latter occurring around the third or fourth day, sometimes even as late as the sixth or seventh day. The control curve on top was obtained from an average of six patients hospitalized and fed under the same conditions as the other patients whose curves

are shown in this graph, the only variable being that no operation was performed on the patients used as controls. The control curve, in contrast with curves 1 to 6, shows a remarkable constancy of the heparin tolerance for 5 days. In Fig. 6, the postoperative heparin tolerance curves of six other patients are shown. In these, the impressive feature is the poor heparin response, particularly in Cases 5 and 6, without an appreciable rise except in Case 2, where a surprisingly delayed rise occurred on the eighth postoperative day. Generally speaking, these curves show much less fluctuation, especially toward the anticoagulant side. The average age of the first group, shown in Fig. 5, is 46 years, and of the second group, shown in Fig. 6, is 55 years, but the first figure is weighted by an unusually vigorous, 72-year-old Scot.

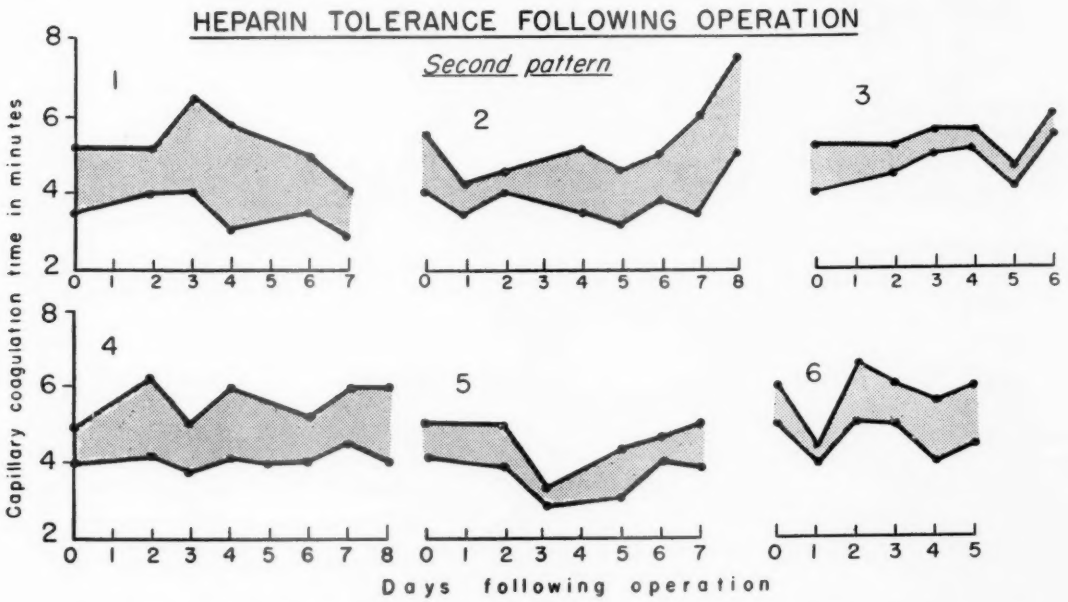

Fig. 6.—(*1*) A. S., age 65 years, diabetic arteriosclerosis, lumbar sympathectomy under spinal anesthesia; (*2*) J. S., age 64 years, generalized arteriosclerosis, amputation of lower leg under spinal anesthesia; (*3*) A. B., age 62 years, generalized arteriosclerosis, lumbar sympathectomy under spinal anesthesia; (*4*) S. H., age 52 years, arteriosclerosis of lower extremities, lumbar sympathectomy under spinal anesthesia; (*5*) H. L., age 57 years, causalgic state of left hand, dorsal sympathectomy, intratracheal anesthesia; (*6*) J. A., age 55 years, obliterating arteriosclerosis, bilateral sympathectomy.

To see whether or not this postoperative fluctuation is part of the general adaptation syndrome as measured by the eosinophil count, a few curves are shown in which eosinophil counts and clotting times sensitized in vitro with heparin have been determined daily (Fig. 7). Here again, the younger and more fit the individual, the greater the response. The reaction of these two mechanisms is not simultaneous, but the fall, rise, and fall of both curves is unmistakable. The only exception to this simultaneous fluctuation of both eosinophil count and sensitized clotting time is shown in the Case of L. S. (Fig. 8), in whom the eosinophils show an excellent response to operative stress, but the clotting mechanism was unresponsive. This curve belongs to a

32-year-old sclerodermatous patient who developed multiple and massive thromboses following therapy with cortisone. That her pituitary-adrenal mechanism was responsive is indicated by the eosinophil response to the operation, but her clotting mechanism was refractory. Since in young, healthy individuals both epinephrine and operative trauma are effective stressors of the clotting apparatus, this is a significant curve. In order to test the similar

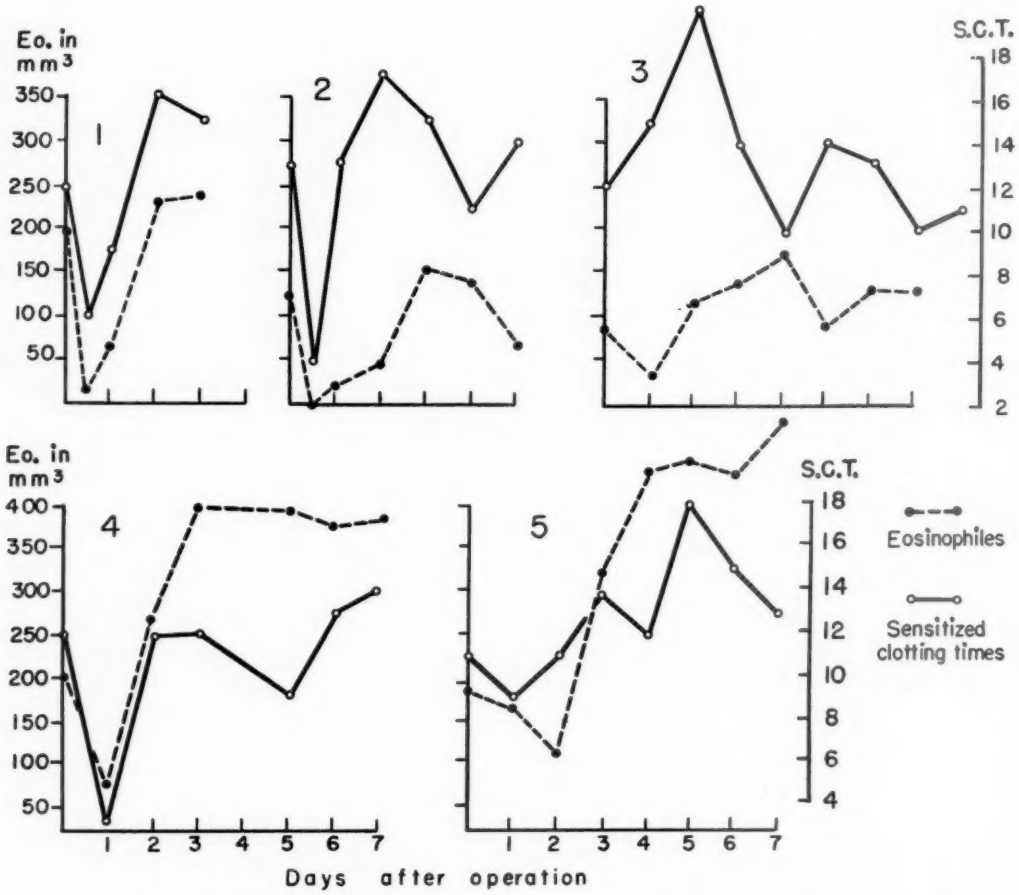

Fig. 7.—Simultaneous daily clotting times and eosinophil counts following operation. (*1*) P. B., age 61 years, Ca. common duct, one-stage Whipple operation; (*2*) E. A., age 52 years, essential hypertension, right lumbodorsal sympathectomy; (*3*) E. J., age 51 years, endarteritis obliterans, midmetatarsal amputation under spinal anesthesia; (*4*) M. E., age 35 years, essential hypertension, second stage splanchnicectomy; (*5*) Ch. M., age 58 years, obliterating arteriosclerosis, lumbar sympathectomy under spinal anesthesia. Note that generally the eosinophil counts lag behind the sensitized clotting times, but their trend is the same.

response of eosinophils and clotting times in another way, 50 mg. of heparin were injected intravenously into L. D., a 32-year-old patient with thrombophlebitis. The response of the sensitized clotting times and eosinophils is shown in Fig. 9. While the peak of the eosinophil count was reached in the first half hour, the clotting times lagged behind. At the peak the rise of the eosinophils was 230 per cent and that of the clotting time was 198 per cent. This same lag was observed in Fig. 7.

A scatter graph of pre- and postoperative sensitized clotting times (Fig. 10) indicates the trend of a postoperative rise of the clotting times with a return to the base level in five to six days. An occasional preoperative lowering might well be due to anxiety, and attention should be called to Macht's report[16] of certain apprehensive or highly nervous blood donors in whom clotting times were short just before donating blood; and to the findings of Schneider,[17] who noted a shortening of clotting times in siliconized tubes after stressor stimuli. The postoperative rise around the second to

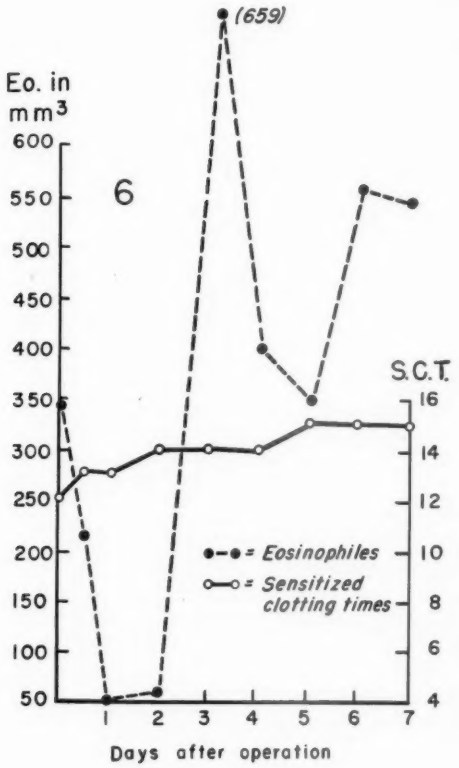

Fig. 8.

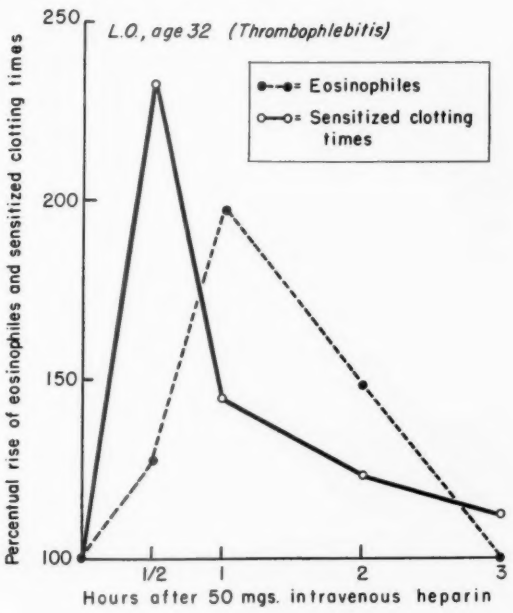

Fig. 9.

Fig. 8.—Case 6, L. S., age 32 years, scleroderma, gangrene following cortisone, toe amputation under general anesthesia. Note the excellent response to eosinophils with no response from the clotting mechanism.

Fig. 9.—Patient L. O., 32-year-old man, who received 50 mg. of heparin at 0 hour intravenously. Sensitized clotting times and eosinophil counts were determined at 0, ½, 1, 2, and 3 hours. The rise is expressed in percentage of preinjection level. Note the earlier and sharper rise of the clotting time. Possibly the methods of determining eosinophil counts are not as sensitive.

fourth day seems to be higher when the individual is young, or when the surgical trauma is more extensive. Thus in Fig. 11 a marked shift of the clotting mechanism takes place and this is accentuated when two operations succeed each other within a few days (Fig. 12).

Nevertheless, not all patients respond with a lengthening of the sensitized clotting time after operation. Fig. 13 shows a graph of six patients in whom

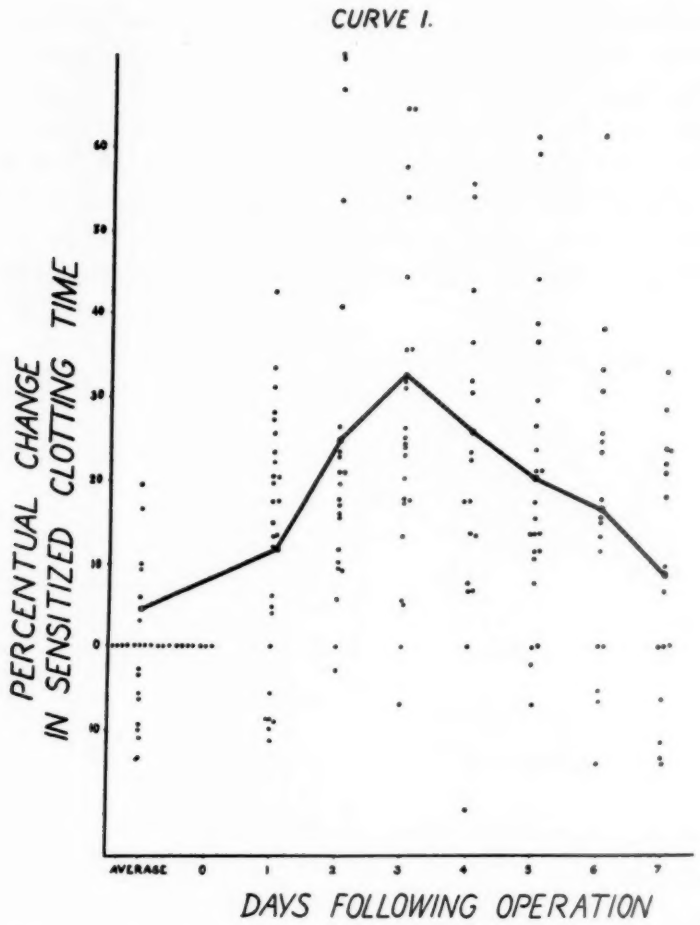

Fig. 10.—Daily sensitized clotting times following operation. In this group the tendency to hypocoagulability of the blood as a response to postoperative stress is unmistakable. The peak of the mean curve is on the third postoperative day. Continuous line represents the mean of thirty-six individual curves.

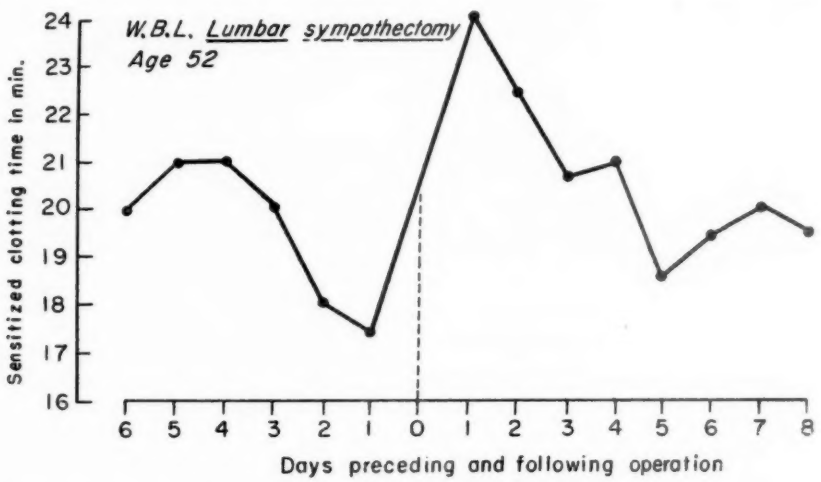

Fig. 11.—Note the preoperative dip of the clotting time followed by a marked rise following operation, a normal response. Spinal anesthesia was used.

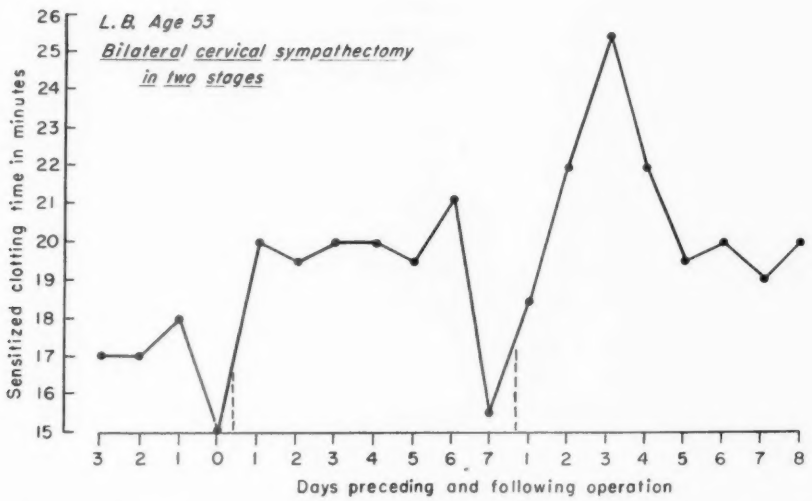

Fig. 12.—The effect of a two-stage operation on the clotting mechanism. Note the increased response after the second operation. Both operations were done under local anesthesia with intravenous Pentothal Sodium.

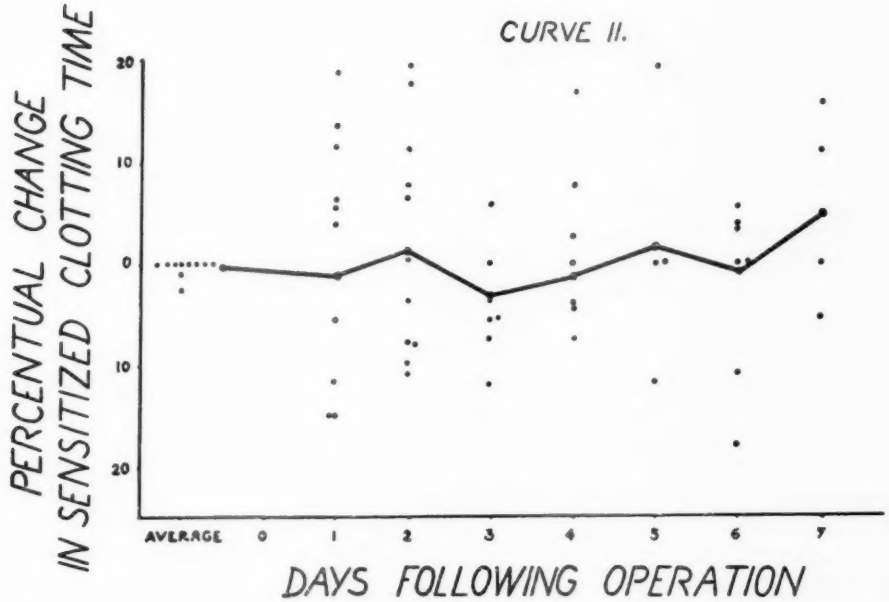

Fig. 13.—Sensitized clotting times following operations. In this group of six patients the clotting mechanism responded to surgical trauma with no rise, and occasionally a fall of the clotting time.

the clotting mechanism was refractory to surgical trauma. We do not know whether such a finding requires prophylactic anticoagulant therapy; we do know, however, that a single intramuscular dose of 200 mg. of heparin in gelatin provides a clotting curve (Fig. 14) similar to that seen in Fig. 10 as a desirable bodily response to surgical trauma.

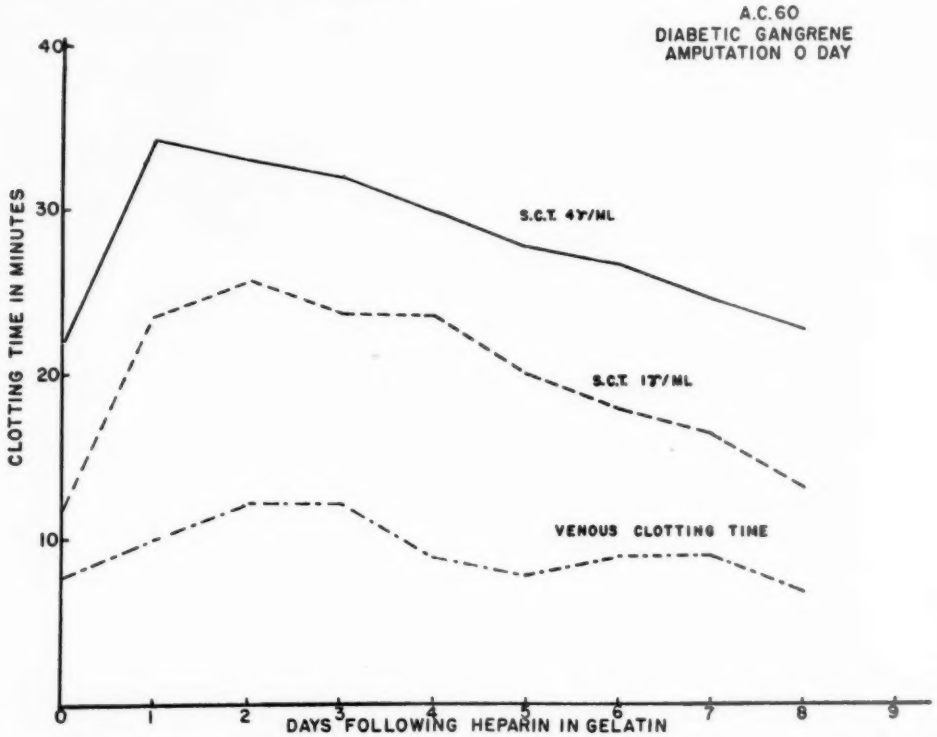

Fig. 14.—Sensitized clotting time. The effect of 200 mg. of heparin in gelatin with vasoconstrictors on a single-tube Lee-White clotting time, and on clotting times sensitized with 1 gamma and 4 gamma of heparin. Note that there was a demonstrable effect on the sensitized clotting times for eight days. (From de Takats, Angiology 1: 317, 1950.)

DISCUSSION

The data presented raise several questions. Is the preoperative response of the clotting time to epinephrine a miniature image of the postoperative response? Does the failure of the clotting time to rise four hours after epinephrine or three to four days after operation indicate threatening thrombosis? And finally, does the response of the clotting mechanism and that of the eosinophil count represent an immunologic response and thus become a part of the general adaptation syndrome? Our present data are obviously of a preliminary nature and can simply raise, but not answer, these questions. Regarding the correlation of the "micro-stress" with epinephrine and the postoperative fluctuation of the clotting time, the preoperative study, at best, can only detect the state of the clotting mechanism and its readiness to cope with surgical trauma. It is known that the length and extent of the operation, together with the amount of tissue trauma and blood loss will augment the chances of clinical thrombosis and this, of course, is immeasurable preopera-

tively. Nevertheless, if statistically significant data could be obtained on the meaning of flat or falling clotting curves after epinephrine, one more index of the endangered group would be available.

Our studies were completed when the findings of R. W. Smith and co-workers of the effect of ACTH and cortisone on the increased level of circulating heparin-like material, together with a prolongation of the clotting time, were reported.[18] Their data fit in with our conception that the effect of non-specific stress on the clotting mechanism depends essentially on two factors: (1) the state of the pituitary-corticoadrenal axis, and (2) the available resources of the clotting system to cope with the initial clotting tendency. The second phase of the general adaptation syndrome, the stage of resistance, should normally be manifested by a prolongation of the clotting time. In the case of L. S., shown in Fig. 8, six weeks of uncontrolled cortisone therapy exhausted this mechanism, led to multiple thromboses, and resulted in a flat postoperative clotting curve.

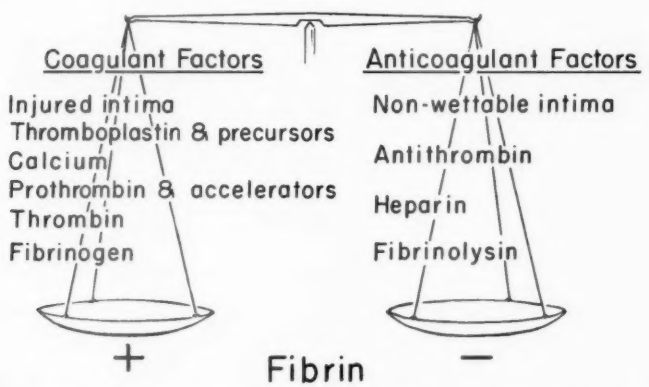

Fig. 15.—The clotting equilibrium. A continuous shifting of the balance toward the coagulant or anticoagulant side may be demonstrated by a sensitized clotting time without the clinical manifestations of thrombosis or hemorrhage. This is a homeostatic mechansim which is subjected to stress after an operation.

In a recent report, Cosgriff and his co-workers[19] stated that both ACTH and cortisone may cause a hypercoagulable state. Ten of their 145 patients treated with one of these drugs developed thromboembolic phenomena. In a master's thesis Nelson[20] showed that in the dog, the administration of ACTH resulted in an increased incidence of experimental venous thrombosis, produced by a combination of trauma and partial constriction. In addition, a decreased clotting time and an elevated platelet count were demonstrable.

From a practical standpoint, sensitized clotting time determined before operation, three to four days after operation, and on discharge from the hospital is a good estimate of the reactivity of the clotting mechanism to stress. Since a 10 per cent fluctuation of the clotting time seems to be within the limits of error of the method, the arbitrary dividing line of 20 per cent rise was adopted to be well outside spontaneous fluctuation or methodological limitations. Further accumulation of such data is now in progress.

Clinical experience shows that patients who leave the hospital after a smooth, uneventful convalescence may return months later with collateral pat-

terns of veins in the lower extremities, which leave no doubt that a deep calf, vein thrombosis has occurred. Such subclinical thromboses may give a poor response to the stress of epinephrine, or to the operation, but will not be included among the cases of manifest thromboembolic disease.

The fact that heparin itself elicits an eosinophil response is intriguing. It has been, of course, known that heparin combines with the serum complement,[21] that it inhibits hypersensitivity reactions,[22] and that it prevents the release of histamine into plasma from the erythrocytes on addition of an antigen.[23] According to Magerl,[24] heparin produces a strong immune reaction by increasing antibody production, and its main function is to produce a physiologic defense against infection. In this sense it would be an aid to the patient in the stage of resistance of the three-phase adaptation syndrome. Thus, a few prophylactic doses given to patients with a poor clotting response seem logical.

Obviously then, more questions are raised than answers supplied by our data. But we have felt justified in registering observations which indicate marked fluctuations in the state of the clotting mechanism which can be correlated with the response of the body to stress. The ability of the clotting mechanism to swing right and left of a normal equilibrium may best be depicted by a diagram in which coagulant and anticoagulant factors hold themselves in balance (Fig. 15).

SUMMARY

Postoperative changes in the clotting mechanism have been followed daily by a simple one-tube venous clotting time sensitized with heparin. Both this test and a daily eosinophil count show fluctuations which place the response of the clotting mechanism to surgical trauma among the manifestations of Selye's general adaptation syndrome. An attempt was made to simulate and anticipate this postoperative reaction by determining the response of the clotting time to epinephrine prior to operation. All that can be said to date is that different patterns exist and that young, healthy, normal patients respond to this "micro-stress" with a lengthening of their clotting time, or rapid recovery from its shortening. Further studies are contemplated, based on these initial observations.

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THE SILICONE-TUBE COAGULATION TIME AS AN AID IN THE DIAGNOSIS OF PHLEBOTHROMBOSIS

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THE SEARCH for an objective test that would accurately select those patients who are likely to develop phlebothrombosis following surgical procedures has been prolonged and varied in approach. It has included the employment of various heparin tolerance tests,[1, 2] including the Waugh-Ruddick in vitro test,[3] and examinations designed to disclose changes in the blood antithrombin level,[4] prothrombin time,[5, 6] viscosity,[7] and coagulation time.[8-12]

No test has appeared that has absolute and unequivocal value, and which has been reproducible in the hands of other investigators. This disease is of such an insidious nature, and so falsely benign in its early manifestations, that the alert, responsible clinician must treat many cases with early questionable signs which are not, in actuality, phlebothrombosis.

Since the cost of anticoagulant therapy is still high, this is a real disservice to the patient, if it is actually unnecessary. However, many believe it unjustifiable to take a chance on the "laissez-faire," conservative regimen, and do protect the patient with venous thrombosis by also treating others whose similar, mild leg signs may be due to muscle strain from early ambulation, localized myositis, small hematomas or muscle infarcts in elderly arteriosclerotic patients, etc. A test, therefore, that had real validity in the differential diagnosis of patients with early, mild postoperative leg signs or questionable pulmonary emboli would have real value, even though it could not predict the onset of phlebothrombosis before the fact.

Sandrock and Mahoney[5] reported a high degree of correlation between hyperprothrombinemia and the onset of phlebothrombosis. McClure and his co-workers,[6] however, found that in 258 patients not developing the disease following operation, the test was falsely positive in approximately 45 per cent. On the other hand, in 25 patients who did demonstrate clinical signs, the test was apparently falsely negative in 60 per cent. The results obtained by Loewe and associates,[10] and by ourselves, more nearly agree with the findings of McClure and co-workers than with those of Sandrock and Mahoney.

Shadid[7] states that a simple measurement of changes in blood viscosity will disclose those patients likely to develop phlebothrombosis. This test in our hands has had no correlation with the prediction or diagnosis of the disease.

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Bergquist,[8] using the capillary tube method, has stated that the coagulation time was decreased in some cases of thrombosis, but that this was not regular enough to have diagnostic significance. Cummine and Lyons[9] have reported that the combination of a study of the changes in capillary tube clotting time, when correlated with the appearance of an abnormal fibrinogen, fibrinogen B, had excellent value in predicting the onset of thrombosis. McClure and associates,[6] and Kay and his co-workers[4] were unable to substantiate these findings. Our findings have also differed from those of Cummine and Lyons, and contrary to them, we have found that fibrinogen B, when it was present at the onset of thrombosis, did not always disappear.

The capillary tube method has been shown to reflect changes in blood coagulation less accurately than the Lee-White method.[13] It most certainly contains multiple factors, leading to variation in the clotting time, which have no relation to such changes as may be occurring intravenously. However, we have felt that the rather indefinite end point of the Lee-White test made a shortening of a few minutes in clotting time of no real significance. Loewe and co-authors[10] have stated that the Lee-White test has no real value in the diagnosis of thrombosis.

It is perhaps true, as Ravdin and Kirby[14] have stated, that important and reliable aids to the diagnosis and therapy of this serious problem must await the availability of more fundamental knowledge in this field. However, it seemed to us that as a necessary consequence of a critical change in one of the components of the coagulation mechanism, there might also be a significant shortening of the in vivo and in vitro clotting times. For any test to have real, and also practical, value it must be simple, easily performed by any intelligent physician, and reproducible.

If the unphysiologically-related effect of glass on the coagulation time could be minimized, then a simple coagulation time method might have real merit. Ideally, one should use glass test tubes lined with a nontraumatized vein wall. This goal, though obviously not practical, can be partially approached by coating glass test tubes with silicone solutions, as shown by Jaques and co-workers.[15] Quick and Favre-Gelly[16] have shown also that clotting is markedly delayed by silicone-coated surfaces, and that platelet destruction and prothrombin consumption are markedly reduced. Using glass tubes approaching these in principle, Kadish,[11] and Margulies and Barker[12] have shown a much higher correlation of positive tests with disease than have been recorded previously.

Two and one-half years ago we began a study of preoperative and daily postoperative coagulation time determinations in the silicone-coated tubes. In order to make the study practical, the tests were all done at room temperature, through all changes of season. Patients were selected for study who were most likely to get the disease. Two hundred seventy-three cases were so followed, of whom eighteen developed phlebothrombosis under test observations. Lee-White clotting times, prothrombin times, blood viscosity, and fibrinogen B determina-

tions were also performed. This report concerns itself with a description of these findings, and it will indicate that the silicone-coated tube method seems to have very great diagnostic significance.

METHODS

Silicone Coating Procedure.—The silicones are polymers of dimethyl siloxane which are clear liquids, remarkably stable, resistant to oxidation, and water repellant. They are as water repellant as any hydrophobic material, and are practically inert physiologically.[17]

Chemically clean and dry Pyrex glass tubes, 13 by 100 mm., were used. A 2 per cent solution of DC 200 silicone* (350 centistoke viscosity) in carbon tetrachloride was used. The silicone-carbon tetrachloride solution was poured to the top of the tubes and allowed to stand for one minute. The tubes were emptied and the carbon tetrachloride was allowed to evaporate for thirty minutes, leaving a thin film of silicone on the glass. They were then baked in an oven at 280° C. (536° F.) for thirty minutes. This temperature is lower than that recommended by the manufacturer. However, it was found to give more consistent results, and is attainable in any regular kitchen stove.

The tubes do not need recoating following each use. They are cleansed with a brush and soap, rinsed with water, and allowed to dry by standing. They were found to give consistent results through at least ten usages with each coating. It has not been necessary to discard the tubes, as they may be recoated indefinitely. After each application they may again be used ten times before recoating. These tubes have the same appearance as regular glass tubes and should be plainly marked, with a diamond pencil, to prevent their being used for other purposes.

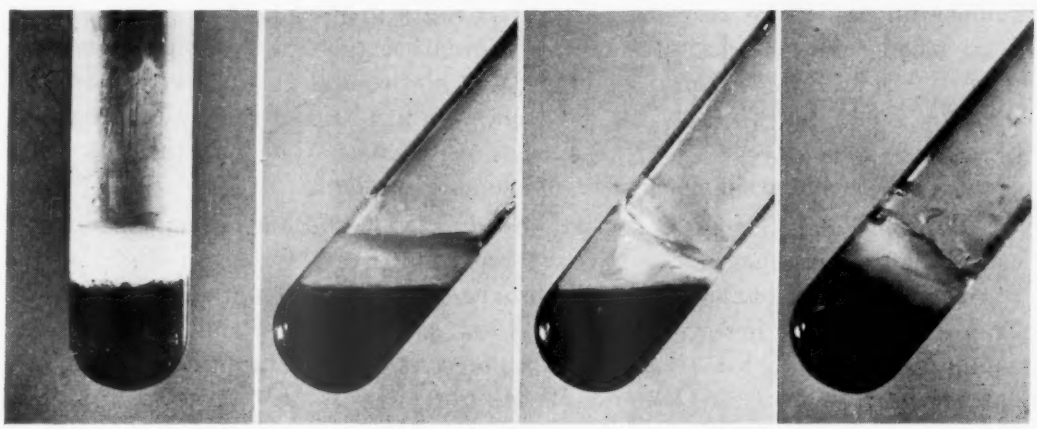
Silicone-Tube Coagulation Time.—A dry syringe was used. Six cubic centimeters of blood were obtained by venipuncture. If the venipuncture was traumatic, the procedure was immediately repeated at another vein, with a clean syringe and needle. The test will always be artificially positive if the vein entry is not perfectly clean. The method is so sensitive that a small amount of thromboplastin, liberated by a traumatic venipuncture, will markedly shorten a normal coagulation time.

One-half cubic centimeter of blood was expelled, and then three silicone tubes were filled with 1.5 c.c. per tube—filling tube No. 3 first, then No. 2, then No. 1. The needle was removed and the blood allowed to flow down the sides of the tubes. The remaining 1 c.c. was discarded. The tubes were left undisturbed for 20 minutes. The blood soon separated into a layer of red cells and one of plasma (Fig. 1, *A*). Tube No. 1 was then picked up and gently inclined until the red-cell mass flowed (Fig. 1, *B*). The same procedure was repeated at 5 minute intervals until the red-cell mass stopped flowing. The plasma will not flow as long as the red-cell mass, because the plasma will coagulate at the interface between air and plasma (Fig. 1, *C*). At first the red-cell mass is very liquid and flows readily, but as the end point is approached, the red-cell mass becomes

*This solution was supplied through the courtesy of the Dow-Corning Corporation, Midland, Mich.

more viscid and flows sluggishly. Just before the end point is reached, the red-cell mass will flow in the center but not around the periphery. Beyond the actual end point, a narrow, tonguelike projection of red cells may continue to flow, even though the main mass of red cells has coagulated. When the red-cell mass does not flow, this is considered the end point (Fig. 1, *D*). The same procedure is then carried out with tubes No. 2 and No. 3. The silicone-tube clotting time was that time at which the end point was reached in tube No. 3.

Modified Lee-White Coagulation Time.—The same method was followed here in the filling of three uncoated 13 by 100 mm. glass tubes. Tube No. 1 was examined at the end of 5 minutes, and at 5 minute intervals thereafter until the end point was approached. It was then examined every minute. As a general principle, we believe the tubes should be agitated as little as possible because such agitation artificially decreases the coagulation time. In doing coagulation times on such blood, which does not separate into layers, the end point is read when the blood ceases to flow when the tube is inclined. There is



A. *B.* *C.* *D.*

Fig. 1.

a tendency for the blood at the interface between air and blood to coagulate before the remainder of the blood coagulates. It is permissible to "flick" gently the tube to break up this surface film, and the blood will then flow freely. However, clotting will usually occur within 3 to 4 minutes after the tube has been "flicked." Normal coagulation times by this method vary between 10 and 20 minutes.

Fibrinogen B Determination.—Fibrinogen B was determined according to the method described by Cummine and Lyons.[9] Oxalated blood was used. One cubic centimeter of the plasma was placed in a clean, dry test tube and 5 drops of 2 per cent betanaphthol in 50 per cent alcohol were added. It was then allowed to stand for 10 minutes, after which tilting the tube was necessary to cause thorough mixing. The formation of a gel was considered a positive test. The positive tests were graded from one plus to four plus, according to the heaviness of the gel. Cloudiness in the solution was not considered a positive test.

Prothrombin Determination.—The prothrombin times were performed in our clinical hospital laboratory according to the Quick method.[16] Undiluted plasma was used, and the normal time was 14.5 seconds. These were performed by the same technician on all occasions.

Blood Viscosity Measurement.—A Hellige viscosimeter (No. 1,200) was used. Through a 26 gauge hypodermic needle, 2 drops of sodium heparin were placed in a glass test tube. Three cubic centimeters of the patient's blood were obtained and mixed with heparin. The viscosity was measured in the viscosimeter, using distilled water as the reference liquid. All relative viscosities were then changed to absolute viscosities by corrections based on room temperature.

RESULTS

Two hundred seventy-three patients were studied preoperatively and throughout their postoperative course with daily silicone tube coagulation times. Eighteen of these developed evidence of phlebothrombosis. A sufficient number of cases were also observed for changes in fibrinogen B, prothrombin time, blood viscosity, and Lee-White coagulation time to evaluate these procedures. In addition to those followed daily, all hospital patients who developed signs or symptoms which would lead one to consider the diagnosis of venous thrombosis were checked for the silicone coagulation time. A total of 3,579 silicone tube coagulation times were done on 364 patients.

Silicone-Tube Coagulation Time Studies.—The normal preoperative silicone coagulation times in the 273 patients studied are shown in Fig. 2. Approximately three-fourths of the patients had times between 60 and 89 minutes. There were several lower, with some as low as 50 minutes, and a few as high as 150 minutes. In the 7 cases, or 2.9 per cent of the total, with normal preoperative times between 50 and 59 minutes, almost half developed phlebothrombosis postoperatively. This small per cent with preoperative times in this low range would bear close scrutiny and perhaps had best be followed with daily postoperative silicone coagulation time determinations. The probability of subsequent thrombosis in those patients who have normal times in the next higher range seemed no greater than in any other group.

Eighteen of the 273 cases developed signs and symptoms which very definitely indicated the diagnosis of phlebothrombosis. This represents an incidence of 6.5 per cent postoperative venous thrombosis in these cases followed daily. The 273 patients were so selected that a high incidence of intravascular clotting might be anticipated postoperatively. In all except one of these 18 cases the silicone-tube coagulation time was 45 minutes or below on the day that the thrombosis was diagnosed, as contrasted with a much higher time the previous day. In that one instance, the patient's coagulation time was 50 minutes, and his leg signs were minimal and very equivocal. He was put to bed and 12 hours later his time was 40 minutes and the leg signs had progressed. Seventy-three per cent of these 18 positive cases had silicone coagulation times between 35 and 45 minutes; 17 per cent had times between 30 and 34 minutes; and 10 per cent, between 20 and 29 minutes.

Two hundred fifty-five of the 273 cases followed daily did not develop signs of postoperative intravascular clotting. The lowest coagulation time, following operation, of three-fourths of these patients was between 60 and 89 minutes (Fig. 3). Seventeen per cent of them had their lowest postoperative time between 50 and 59 minutes. However, the great majority of these were at 55 minutes, and were there for a single determination only. Furthermore, this test is sensitive enough, and the end point is clear enough, for accurate division between the normal and abnormal times which fall in this close range. One must, however, avoid such pitfalls as traumatic venipuncture and excessive agitation of the tubes which will artificially shorten the coagulation time. For a test to be considered positive, the coagulation time must remain at, or below, the 45 minute level for 12 hours.

FIG. 2.

NORMAL PREOPERATIVE SILICONE TUBE COAGULATION TIME

RELATION TO DEVELOPMENT OF POSTOPERATIVE PHLEBOTHROMBOSIS (273 PATIENTS)

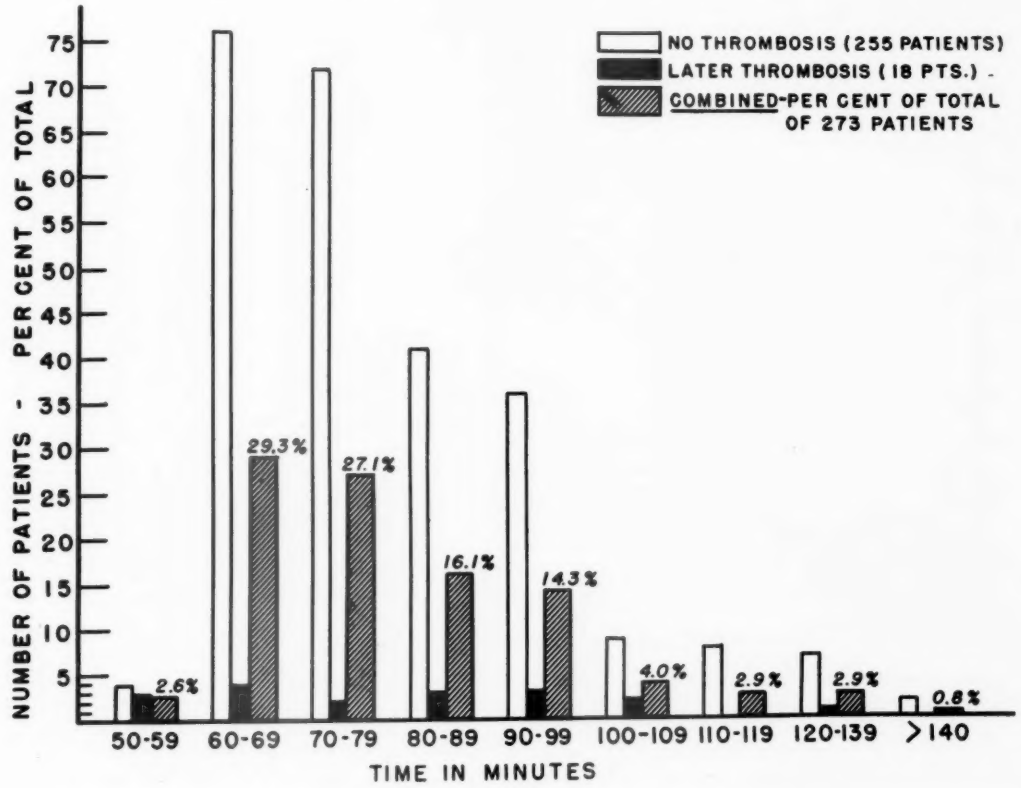
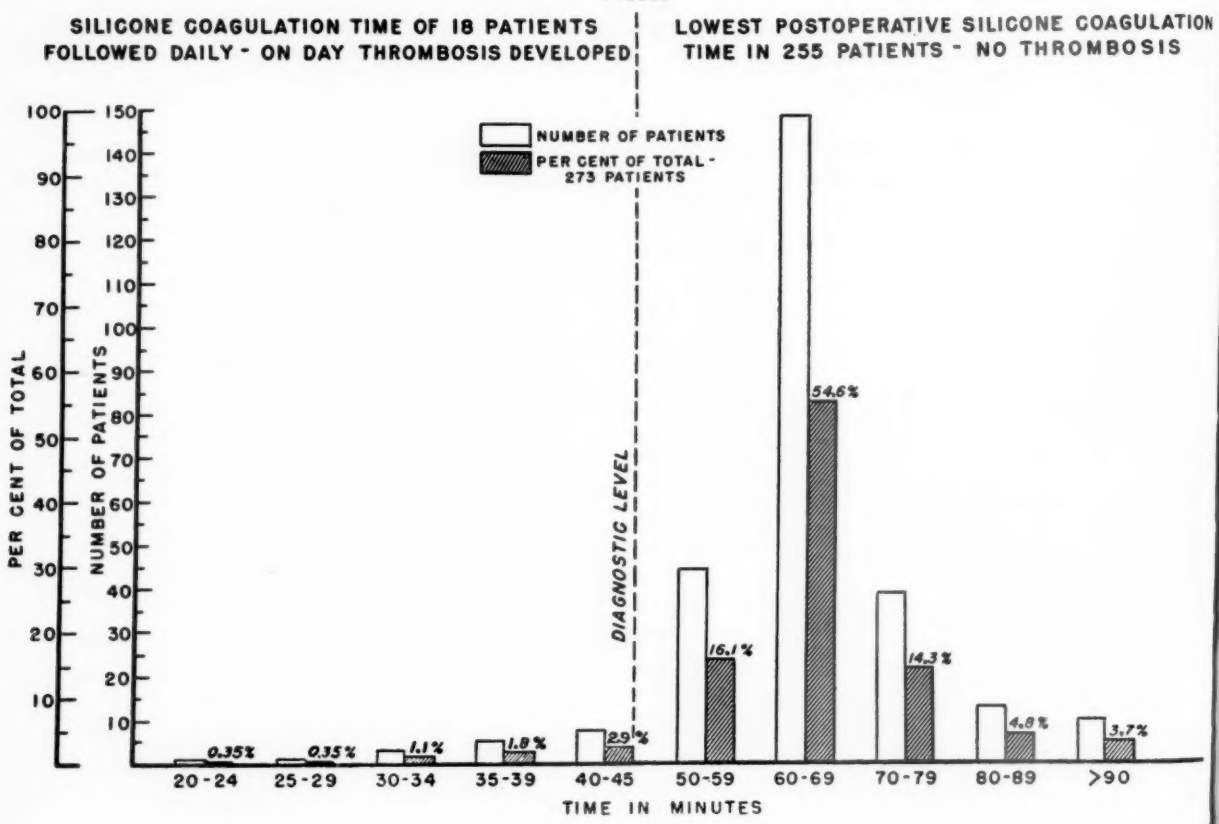


Fig. 4 shows the postoperative day on which the lowest coagulation time occurred in those patients not developing phlebothrombosis. Four-fifths of these patients had their lowest time in the first 4 days. The curves of the silicone coagulation times, during the first 4 postoperative days, were also analyzed. A gradually increasing clotting time was observed in 48 per cent of those cases who did not develop thrombosis, and in 29 per cent of those who did.

The curves declined in 33 per cent of those who failed to develop thrombosis, and in 55 per cent of those who did develop it. The curve was flat, without significant rise or fall, in 19 per cent of the former, and 17 per cent of the latter. There was, thus, no significant difference in the first four days between those who developed thrombosis and those who did not. Consequently, it would not seem that the daily performance of this test would have any predictive value—Fig. 5 demonstrates that the clotting time was in perfectly normal ranges on the day before the disease was manifest.

FIG. 3.



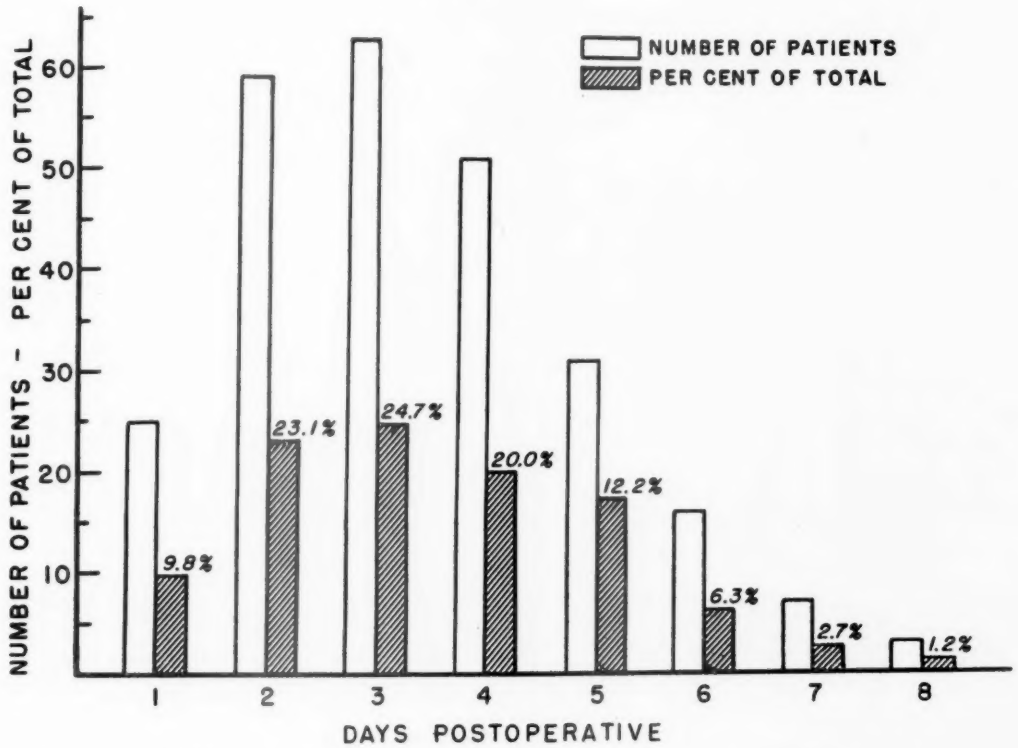
All of our hospital patients not in this study group, and many in other local hospitals, who had developed signs or symptoms which would lead one to consider the diagnosis of phlebothrombosis or pulmonary embolus, were "spot-checked" for their silicone clotting time. There were 65 patients in this group. Thirty of these had positive spot-checks of 45 minutes or below. It was of importance to note that, even in those cases with severe chest signs suggestive of pulmonary embolism, and minimal to absent leg signs, the silicone clotting time was below 45 minutes. In several cases of obvious pneumonia and atelectasis the time was normal. Seventy-two per cent of these 30 patients had coagulation times between 35 and 45 minutes, 3 per cent had times between 30 and 34 minutes, and 25 per cent between 20 and 29 minutes. It was believed that these

cases had a pulmonary embolus and/or phlebothrombosis and they were treated with heparin or venous ligation. The other 35 were assumed to have some other cause for their minimal leg signs and were not actively treated. The follow-up study of these 35 cases is given later.

Three patients had therapeutic vein ligations and clots were removed from the vein at operation. Fig. 6 shows the course of the silicone coagulation time in these patients. The time remained in the abnormal range for 3 days following the onset of thrombosis in one case, for at least 3 days in another, and for 5 days in the third. Seventeen of the 30 patients were spot-checked on the first

FIG. 4.

POSTOPERATIVE DAY OF LOWEST SILICONE COAGULATION TIME IN 255 PATIENTS - NO THROMBOSIS



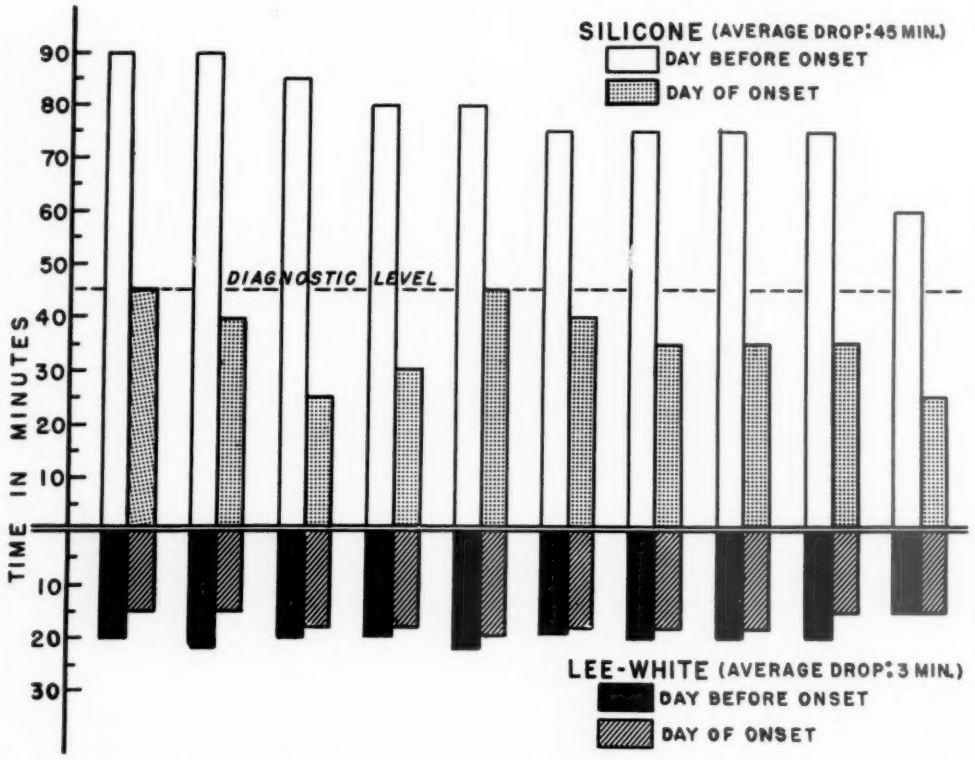
day the signs and symptoms developed, and were found then to have positive tests. Of the remainder, 5 patients still had positive tests on their second day of disease; 4 on the third day; 1 on the fourth day; and 1 on the fifth day. Two patients had a coagulation time below 45 minutes even on the sixth day of their disease. This is in contradistinction to the statement of Cummine and Lyons[9] that the coagulation time tends to rise to normal coincident with the development of phlebothrombosis.

In the other 35 cases, not being followed daily, who were spot-checked because of the development of signs suggestive of either phlebothrombosis or pul-

monary embolus, the silicone coagulation times were well within normal range. These patients, along with 12 of the group being studied daily, who also had developed minimal leg signs suggestive of thrombosis, were treated only by bed rest, because they had normal silicone coagulation times. All 47 patients had mild leg signs, characterized by slight to moderate tenderness, no increase in leg circumference, no edema, and only questionable consistency changes. The vast majority of these cleared on 12 to 24 hours of bed rest. Others went on to develop clear-cut signs of myositis, frequently localized to one gastrocnemius head, or muscle hematoma, cellulitis, or obvious superficial thrombophlebitis. It was true that in the early phases their signs were indistinguishable from phlebothrombosis. All of the 47 were then checked daily and the silicone clotting time remained normal.

FIG. 5.

COMPARISON OF SILICONE AND LEE-WHITE COAGULATION TIMES DAY BEFORE AND DAY OF ONSET OF PHLEBOTHROMBOSIS (10 PATIENTS)

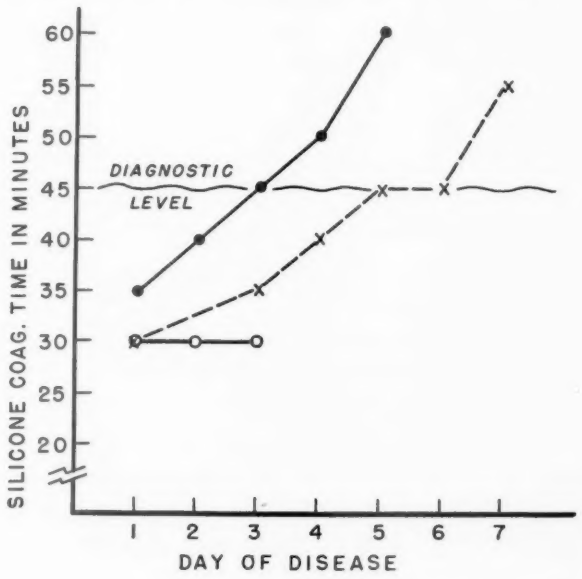


All but 1 of these 47 patients were examined in the hospital several months after the diagnostic question arose. One hundred eighty-three of the group of patients studied daily who did not develop any signs suggestive of thrombosis have had similar follow-up examinations. The remaining 60 of this latter group have been contacted by letter and 35 responded. No late evidence of intravascular clotting had appeared at any time in any of these patients, nor had a pulmonary embolus occurred.

Forty other patients had such minor leg complaints that a diagnosis of phlebothrombosis or thrombophlebitis could be ruled out on a purely clinical basis. As a matter of interest, they were also checked with the silicone tubes, and all had normal times. It was extremely interesting to find the silicone coagulation time, in all 25 cases of unquestionable superficial or deep thrombophlebitis, within normal limits. This offers another basis for the opinion that thrombophlebitis and phlebothrombosis are entirely different diseases.

Lee-White Coagulation Time.—The coagulation time of blood in the usual uncoated glass test tubes was studied by means of the 3 tube, modified Lee-White method—1,866 tests being done on 200 patients. In 10 patients being studied daily, who developed signs of thrombosis, simultaneous coagulation times were determined by the modified Lee-White and silicone tube methods. Fig. 5 shows a comparison of the coagulation time on the day before, and the day of, onset

FIG. 6.
3 PATIENTS WITH PHLEBOTHROMBOSIS
(CLOT FOUND ON FEMORAL VEIN LIGATION)
DURATION OF SUBNORMAL CLOTTING TIME



of intravascular clotting. There is an average drop of 45 minutes in the silicone coagulation time as compared with an average of only 3 minutes in the Lee-White coagulation time. The 3 minute drop in the latter method is certainly well within the limits of error of the test. Its end point is never definite, and a greater variation than 3 minutes is frequently found in those never developing the disease, when determinations are done daily. Nothing of significance was found in coagulation times done by this method that would aid in either the prediction or diagnosis of phlebothrombosis.

Blood Viscosity Changes.—Similar equivocal results were obtained in the study of the blood viscosity determinations, performed 680 times in 85 post-

operative patients. Twenty-five per cent of the cases followed daily, who did not develop thrombosis, had increases in viscosity greater than any of those who developed thrombosis. Fifty-seven per cent of the cases without thrombosis had greater increases in viscosity than the average increase of those who developed the disease.

Fibrinogen B Determinations.—These were done 3,579 times in 364 patients, simultaneously with the daily silicone clotting times. No correlation of significance between the occurrence of intravascular clotting and the positive tests could be found. In the patients followed daily, fibrinogen B was found at least once in 33 per cent of those who did not develop thrombosis, and in only 39 per cent of those who did. Fibrinogen B was likewise found in very similar proportions of the spot-check examinations. There were positive fibrinogen B tests in 41 per cent of those with thrombosis, and in 39 per cent of those without. This also is contrary to the report of Cummine and Lyons[9] who stated that fibrinogen B disappears when phlebothrombosis begins. In our experience it frequently persists for 1 to 2 days, even after heparin therapy has been under way.

Prothrombin Time Determination.—Two hundred forty examinations were performed on 53 patients, who were studied daily. The occurrence of hyperprothrombinemia in the first 4 postoperative days has previously been said to be of significance in the prediction of postoperative phlebothrombosis.[5] Forty-two per cent of our cases had hyperprothrombinemia in the first 4 postoperative days, and none of these developed phlebothrombosis. No patient happened to develop thrombosis while being followed daily. However, it seemed that such a high incidence of hyperprothrombinemia (42 per cent), in the no-thrombosis group, would destroy any possible predictive value of the test. This finding corresponds closely to the incidence of 45 per cent, reported by McClure and co-workers[6] in their patients who did not develop clinical signs.

DISCUSSION

Daily silicone-tube coagulation times and fibrinogen B determinations were performed postoperatively on all of 273 patients. In addition many were examined daily for changes in the Lee-White clotting time, blood viscosity, and prothrombin time. Only the silicone coagulation time seemed to have diagnostic value in the clinical problem of phlebothrombosis and pulmonary embolization.

Unfortunately, even the latter appeared to have no predictive value. The silicone clotting time in all 18 patients who developed phlebothrombosis under test observation was perfectly normal on the day before the disease occurred. The average drop from the level on the day before the onset, to that on the day of the appearance of signs, was 45 minutes (Fig. 5). Relatively few of those that did not develop signs ever had a postoperative silicone clotting time below 60 minutes. All 18 of the patients who developed leg signs, and were treated for the disease, had clotting times of 45 minutes or below (Fig. 3). It was true, however, that when this drop had occurred in the coagulation time, the leg signs were still minimal and were always confined to the veins below the knee. None

had pulmonary emboli before or after heparin therapy was begun. Viewed in this light the daily use of this method would have real merit in the early diagnosis of venous thrombosis. Treatment at this opportune period would have the value of preventing many pulmonary emboli and the late, severe symptoms of obstructive venous origin. From the practical standpoint, few busy surgical services could so follow all of their postoperative patients.

The blood in silicone-coated tubes settles out, in a similar manner to well-heparinized blood (Fig. 1). This results in a clear-cut end point which can be accurately determined. Since the test is very sensitive, the details of the method must be diligently observed or false positives will occur. The diagnostic level is at 45 minutes. All patients that we were relatively certain had venous thrombosis had clotting times below this point. Even a moderately traumatic venipuncture will cause an artificial shortening of the time. In another study,[18] we found that the clotting time of a small percentage of patients, given test dosages of penicillin, fell below the 45 minute level. One must wait at least 3 hours after an intramuscular injection of 100,000 units of penicillin before the test will have real validity. Consequently, when the diagnostic question arises this must always be considered. Furthermore, before considering a test positive, we have immediately repeated the test and placed the patient at bed rest. A third check is carried out 12 hours later, and if all are 45 minutes or below, we have actively treated the patient. There is no doubt that extremes of temperature have a marked influence on these clotting times.[15, 16] However, with room temperatures ranging from 72° to 90° F., we have had no reason to suspect that this factor has had practical significance. Even at the lower end of that range of temperature, the coagulation time has always been at 45 minutes or below when the clinical picture strongly suggested thrombosis. However, with temperatures of 95° F. or above, it may be necessary to lower the level of significance to 40 minutes. If these variations in the room temperature were critical, then one would expect the highest incidence of positive tests to occur in the warm months. However, our lowest incidence of phlebothrombosis, with the final diagnosis based on the clotting time, has been in the warmer summer months. At the lower extreme of room temperature false negatives might appear. Our follow-up study disclosed no such instance of a patient developing late signs of thrombosis or embolism.

Early in the program, a case had been considered a false positive because of the absence of leg signs. This patient returned a short time later with a swollen leg and signs typical of phlebothrombosis. As our confidence in the test increased, we felt impelled to treat all those with positive tests. It was realized that this would cast doubt on the validity of our later "positive" cases, but the potentially catastrophic sequelae of this disease seemed to justify this attitude. This approach to meeting the clinical responsibility should result in treating only a few cases unnecessarily. The occurrence of many false positive tests would be accompanied by an artificially high recorded incidence of phlebothrombosis.

During the two and one-half year period of this study, 4,836 patients were operated upon under spinal or general anesthesia. Eighteen cases of phlebothrombosis developed in the test group of 273 cases—an incidence of 6.5 per cent. Although this is high, the patients selected for daily observation were those who were known to be prone to develop thrombosis. McClure and his associates reported 25 cases in 283 patients followed in one group and an incidence of 18 per cent in another selected group.[6] In addition to the 18 cases in the test group, 16 cases developed in our other postoperative patients. The development of 34 cases of phlebothrombosis, in this total of 4,836, gives an over-all incidence of only 0.7 per cent. This rate is quite low and compares favorably with the many reports in the literature. It would seem, therefore, that basing diagnosis on such an objective test, properly performed, would not lead to excessive unnecessary therapy.

False negative tests would have very serious consequences for the patients; therefore, an intensive follow-up was conducted of all those who had negative tests. This included patients who never had developed signs, but special attention was concentrated on those that had had some complaints with their legs in the postoperative course. Twelve of the 255 patients who never developed a positive test postoperatively fitted into this latter category. In addition, 35 patients of the 65 spot-checked because of leg complaints, had negative tests. (This group of 65 was composed of patients on the surgical service but not in the daily test group, patients on other services, direct admissions, and cases in other hospitals.) All but one of these 47 were personally examined, months later, and none had had a pulmonary embolus nor were there any late signs of venous thrombosis. When the signs or symptoms had developed, this group of patients was placed on bed rest and followed very carefully, without other treatment. In the great majority, those with early postoperative complaints and negative silicone tests were free of symptoms in 12 to 24 hours; they were then allowed to become ambulatory under observation. Daily silicone coagulation times were continued and all remained in the normal range. Some went on to develop what appeared to be localized myositis, muscle hematoma, cellulitis, or thrombophlebitis. These patients were also kept at bed rest, local heat was applied, and all of them maintained normal clotting times. In our opinion, all of this small group developed local pathology which did not resemble, nor did it follow the course of, phlebothrombosis.

False negatives might be frequent in those cases which are seen as diagnostic problems several days after onset of the disease. It is important, therefore, to know how long the silicone clotting time remains low after the disease has begun. Fig. 6 offers some evidence in this matter. Although we have observed the clotting time to be still low on the sixth day of symptoms, one of these cases had reached normal limits by the fourth day. It would seem, therefore, that after the third day one would have to place reliance on the physical findings, when clotting time was normal. Fortunately, diagnosis is usually not difficult in cases seen that long after onset.

Margulies and Barker[12] have studied the coagulation time of blood in silicone tubes. They determined a "normal" level and found that 88 per cent of 50 normal subjects were above this point; 18 per cent of 18 cases of thrombophlebitis also were above it. This wide overlap would mean that no absolute clinical reliance could be placed upon the test. In our study we found no normal subject falling below the diagnostic level of 45 minutes, even during his postoperative course. Conversely, all cases believed to be phlethrombosis were below that level. It is important, therefore, to attempt to find reasons for these discrepancies. At the beginning, we also used the General Electric Dri-Film silicone, after the method of Jaques and associates.[15] The tubes were recoated after each use. It was observed, after the third coating of the tubes, that the coagulation times obtained were becoming shorter. No amount of recoating then would result in a return to "normal" coagulation times. After the first few cases the tubes were discarded after the third coating. The Dow-Corning silicone was then studied. For the next 50 cases duplicate determinations were made in both tubes and comparable times were obtained, when the conditions outlined under Methods were fulfilled. Whereas the former had the aforementioned disadvantages, the latter tubes could be washed with soap and water and reused at least 10 times before a second coating was necessary. Furthermore, these tubes have been coated up to 10 times (100 usages) without losing their accuracy. Since Margulies and Barker mentioned that their tubes were repeatedly recoated, the 12 per cent of normal cases, falling into the same category as the disease cases in their study may have shown shorter coagulation times by chance, for this reason.

Eighteen per cent of their 18 cases of thrombophlebitis were in the range of normal. One of these patients had a chemical thrombophlebitis and another was listed as having subsiding thrombophlebitis—both of these had normal clotting times. These two cases would account for most of the 18 per cent falling within normal limits—the former differs in etiology, and the latter in phase of disease, from the usual picture of early phlebothrombosis. We believe thrombophlebitis and phlebothrombosis are entirely different diseases. How many of their other 16 cases might be classifiable as phlebothrombosis was not ascertainable from the data. All 25 of our patients with unequivocal, acute thrombophlebitis had normal clotting times—none of the cases of phlebothrombosis did.

Enthusiasm for the potential value of a test for phlebothrombosis and pulmonary embolus must be tempered by the feeling of responsibility to the patient with this very serious malady. We have developed great confidence in this test and for the past year all differential diagnosis in this field has been based on the silicone-tube coagulation time. In our extensive follow-up study we have not found evidence of a false negative test. More important, during the same interval, there has not occurred one pulmonary embolus in the last 2,000 consecutive postoperative patients. Within the limitations described here we do believe that the test will be of real value when cautiously applied to the problem of the diagnosis of phlebothrombosis and pulmonary embolism.

CONCLUSION

1. The silicone-tube coagulation time was determined daily, postoperatively, in 273 patients. Fibrinogen B, prothrombin time, Lee-White coagulation time, and blood viscosity were also determined daily on many of these patients.

2. Eighteen of these patients developed phlebothrombosis under test observation. All of these had coagulation times below 45 minutes, whereas none of the other 255 patients had any postoperative clotting time that low.

3. All other postoperative cases, not in the study group, were spot-checked if they developed questionable signs. Patients having a positive test were given active therapy. That the false positive rate must have been extremely low is substantiated by an incidence of only 0.7 per cent phlebothrombosis in the 4,836 patients operated upon during the period of this study.

4. An intensive follow-up study of over 90 per cent of 290 patients with negative tests failed to reveal a single false negative result.

5. Of all the types of tests performed, only the silicone-tube coagulation time seemed to be significant. Although the latter had no predictive value, it did appear to have real merit in the clinical diagnosis of early cases of phlebothrombosis and pulmonary embolism.

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SPONTANEOUS THROMBOPHLEBITIS

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A STUDY has been made of a series of 90 apparently healthy individuals in whom thrombophlebitis occurred without being preceded by infection, trauma, heart failure, cancer, operation, or other precipitating episode. Venous thrombosis is commonly considered merely a complication of other disorders. This analysis is designed to study the spontaneous development of phlebitis and the course of the disease when not complicated by other pathologic conditions.

Thirty-five of the cases discussed here were observed at the Ochsner Clinic from 1942 to 1951. Fifty-five were observed, over a twelve-year period from 1938 to 1950, at the Charity Hospital of Louisiana in New Orleans. At the latter institution the cases of spontaneous thrombophlebitis represented 4.5 per cent of the entire series of 1,223 cases of acute venous thrombosis or pulmonary embolism observed during that period of time. Comparisons will be made of the distribution of these cases of spontaneous thrombophlebitis with a previously reported study[21] of the entire series of cases at the Charity Hospital. In the present report the incidence of spontaneous phlebitis is somewhat lower than previously reported because critical re-evaluation eliminated some cases as possibly secondary.

The distribution of venous thrombosis is revealed in Table I. The marked preponderance of involvement of the extremities, particularly the lower, is apparent.

Table II records the relative distribution of cases of spontaneous thrombophlebitis of the lower extremities as compared with the distribution in 677 cases of lower extremity involvement, chiefly secondary, in the twelve-year series of Charity Hospital.[21] It is apparent that bilateral involvement occurred more frequently in spontaneous phlebitis. The right-sided preponderance of superficial phlebitis reversed the usual findings in deep phlebitis and occurred both in the primary and secondary cases. This suggests that whatever factors contribute to the preponderance of left-sided deep thrombophlebitis do not similarly affect superficial phlebitis.

The low incidence of pulmonary embolism reflects the fact that spontaneous thrombophlebitis usually is of the nonsuppurative inflammatory type in which embolism is unusual. A relatively high incidence of superficial vein involvement

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in spontaneous thrombophlebitis is revealed in Table III. The involvement of the superficial veins in 43 per cent of the spontaneous cases was significantly higher than the 16 per cent in the total series.

TABLE I. ANATOMIC DISTRIBUTION

LOCATION	CASES	PER CENT
Right lower extremity	33	37
Left lower extremity	34	38
Both lower extremities	21	23
Right upper extremity	1	1
Pulmonary embolus, unknown primary site	1	1
Total	90	
Associated vein involvement		
Both arms, plus leg	2	2
Dorsal vein of penis, plus leg	1	1
Pulmonary embolism	7*	7.7

*One fatal case.

TABLE II. RELATIVE ANATOMIC DISTRIBUTION SUPERFICIAL PHLEBITIS AND TOTAL PHLEBITIS OF LOWER EXTREMITIES

	SPONTANEOUS THROMBOPHLEBITIS		ALL THROMBOPHLEBITIS (CHARITY HOSPITAL)	
LOCATION	SUPERFICIAL	TOTAL	SUPERFICIAL	TOTAL
Number of cases	27	89	94	677
Right leg	41%	37%	53%	37%
Left leg	33%	39%	44%	49%
Bilateral	26%	24%	33%	14%

TABLE III. INCIDENCE OF SUPERFICIAL AND DEEP VEIN INVOLVEMENT OF LOWER EXTREMITIES

	SPONTANEOUS PHLEBITIS		ALL TYPES PHLEBITIS	
	CASES	PER CENT	CASES	PER CENT
Deep veins	50	56	571	84
Superficial veins	27	30	94	14
Superficial and deep veins	12	13	12	2
Embolus, unknown primary	1	1		

The sex incidence was not remarkable. Forty-seven cases (52 per cent) occurred in men and 43 cases (48 per cent) in women. In the Charity Hospital series 28 cases occurred in white persons and 27 cases in Negroes. This represents an incidence of 13.6 per 100,000 adult admissions in the former group and 10.3 per 100,000 adult admissions in the latter. The comparable figures for the entire Charity Hospital series were 266 and 244 (Fig. 1).

The ages ranged from 13 to 88 years with the highest incidence in the fifth and sixth decades (Fig. 2). It will be observed from Fig. 3 that the age distribution follows the pattern of thromboembolism as a whole with two exceptions. No case of spontaneous phlebitis occurred in childhood, an age when major precipitating factors such as severe infection or dehydration are essential for the development of venous thrombosis. The incidence of secondary thrombophlebitis is higher in the older age groups in which the precipitating factors of heart disease, cancer, and operations are more common.

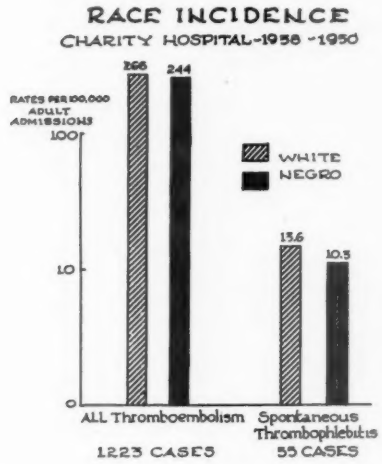

Fig. 1.—Race incidence at Charity Hospital from 1938 to 1950. A comparison between cases of spontaneous thrombophlebitis and all cases of thromboembolism.

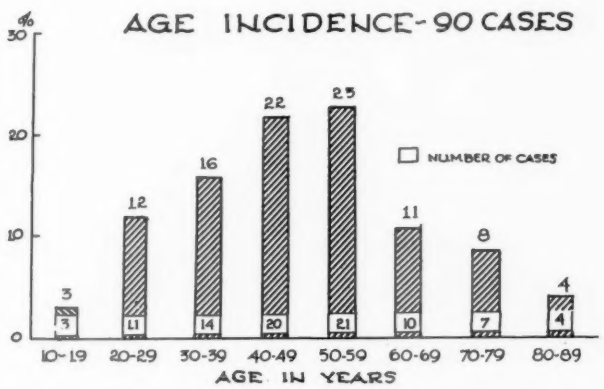

Fig. 2.—Age incidence, by decades, of 90 cases of spontaneous thrombophlebitis.

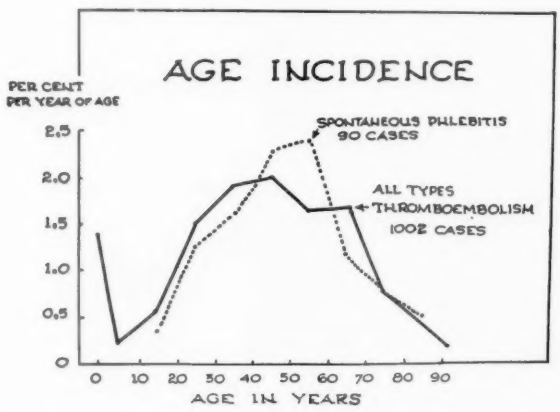

Fig. 3.—Age incidence. Comparison between cases of spontaneous thrombophlebitis and all types of thromboembolism.

An attempt was made to determine factors predisposing to the spontaneous occurrence of thrombophlebitis. Obesity was recorded as present in 25 per cent and absent in 52 per cent, and was not mentioned in 23 per cent of the records. There was no mention of a family history of phlebitis or other vascular disease. Among the patients themselves there were some with other types of vascular disease which did not appear to affect the phlebitis directly. There were 8 with moderate varicose veins, there were 4 elderly patients with arteriosclerosis, and 1 young woman with vasospastic peripheral arterial disease.

Recurrent attacks of phlebitis occurred in 34 cases: 18 cases with deep vein involvement, 13 cases with superficial vein involvement, and 3 cases in which both deep and superficial veins were involved (Fig. 4).

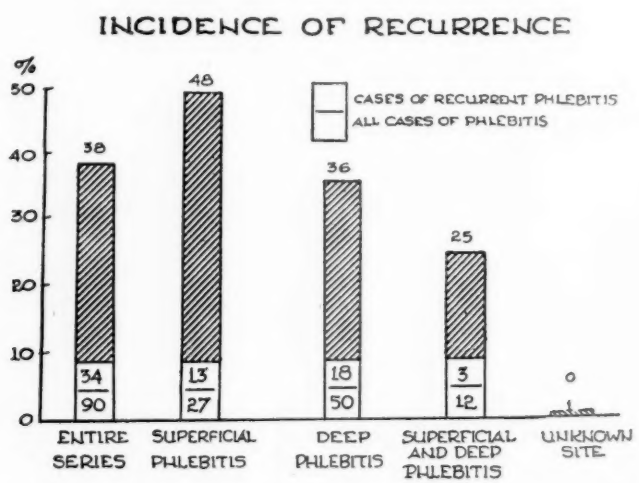

Fig. 4.—Incidence of recurrence of spontaneous thrombophlebitis in superficial and deep veins.

The onset of phlebitis was, in each instance, spontaneous and not preceded by any of the usual precipitating factors. The onset was acute in 30 cases (33 per cent), subacute in 36 cases (40 per cent) and insidious in 24 cases (27 per cent) (Fig. 5). In 9 cases (10 per cent) the first symptoms were noted on awakening in the morning.

Pain was a prominent symptom, although absent in 14 individuals (16 per cent). It was of mild degree in 21 cases (23 per cent), moderate in 40 (44 per cent) and severe in 15 (17 per cent) (Fig. 6). Fever was absent in 38 patients (42 per cent). When present the temperature elevation was not striking in most instances. Temperatures up to 100° F. were present in 31 (35 per cent), up to 102° F. in 17 (19 per cent) and above 102° F. in 4 individuals (4 per cent) (Fig. 7).

Edema was absent in the initial attack of phlebitis in 18 cases (20 per cent). In 11 of these the superficial veins alone were involved. In 25 (28 per cent) the edema was mild, in 31 (34 per cent) it was moderate and in 16 (18 per cent) it was severe (Fig. 8). Tenderness was absent in 13 (14 per cent). It was present chiefly in the region of the calf in 34 (38 per cent), principally

in the region of the femoral triangle in 12 (13 per cent), it was generalized in 22 (24 per cent), and limited to the region of a thrombosed superficial vein in 9 (10 per cent) (Fig. 9).

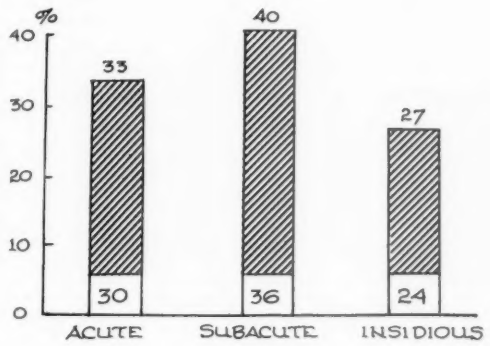

Fig. 5.

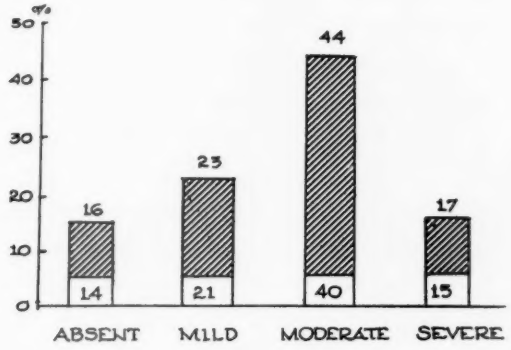

Fig. 6.

Fig. 5.—Type of onset in 90 cases of spontaneous thrombophlebitis.
Fig. 6.—Incidence and severity of pain in 90 cases of spontaneous thrombophlebitis.

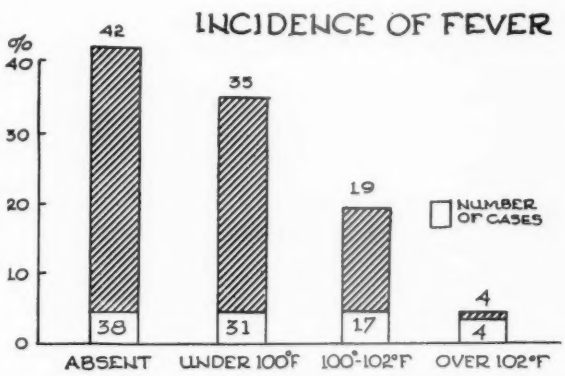

Fig. 7.

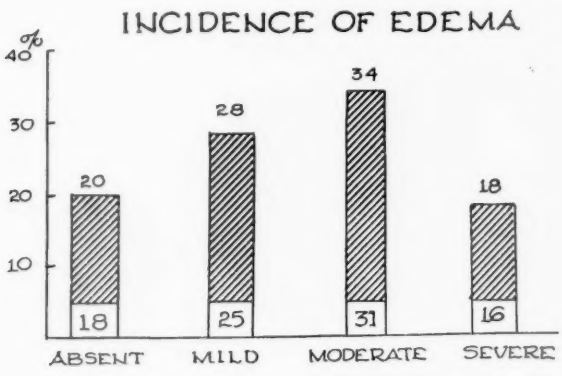

Fig. 8.

Fig. 7.—Incidence and character of fever in 90 cases of spontaneous thrombophlebitis.
Fig. 8.—Incidence and severity of edema in 90 cases of spontaneous thrombophlebitis.

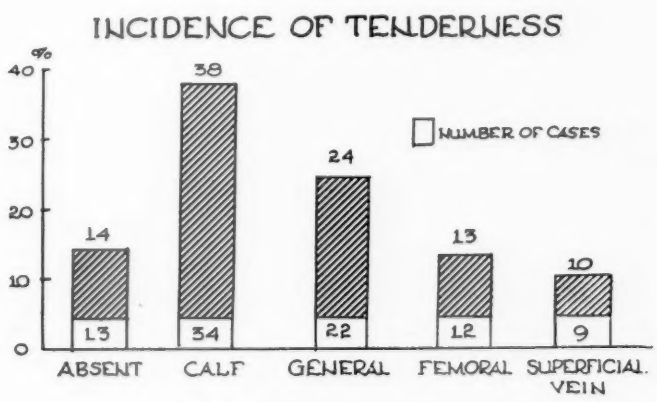

Fig. 9.—Incidence and distribution of tenderness in 90 cases of spontaneous thrombophlebitis.

In general, the clinical picture of thrombophlebitis of spontaneous origin differed little from secondary phlebitis. The incidence of superficial phlebitis was higher, the right leg was more frequently involved, bilateral involvement of the lower extremities was more common, and there was a greater tendency to recurrent attacks (38 per cent).

Numerous forms of treatment were employed, as the majority of the patients were treated on many different services at the Charity Hospital. No attempt will be made to detail the methods of therapy. It is our policy in acute nonsuppurative thrombophlebitis to wrap the extremity in an elastic bandage, to anesthetize the sympathetic nerves to the part one or more times with procaine, and to encourage early ambulation. As vasospasm usually accompanies deep phlebitis, the relief of pain by lumbar sympathetic block is generally dramatic. If the pain recurs the block should be repeated. Edema usually subsides rapidly.[20] The response to sympathetic nerve block in cases of superficial phlebitis is often not remarkable. The local application of heat is usually helpful.

Strict bed rest is avoided as it predisposes to further extension of the venous thrombosis. Periodic elevation of the extremity hastens the subsidence of edema. In the absence of cellulitis or of suppurative thrombophlebitis, there is no indication for antibacterial therapy such as antibiotics or sulfonamides. Numerous investigators have cultured segments of nonsuppurative thrombophlebitic veins, both superficial and deep, and the cultures have been uniformly sterile. An inflammation is present but no infectious agent has ever been incriminated as the cause.

Interruption of the vein proximal to the point of thrombosis is indicated if embolic phenomena have occurred, in suspected phlebothrombosis, or in recurrent thrombophlebitis, because of the high incidence of pulmonary embolism in the latter two groups. As stated previously, the majority of the cases of spontaneous venous thrombosis are of the nonsuppurative thrombophlebitic type in which embolism is infrequent and rarely fatal.

Pulmonary embolism occurred in 7 cases (7.7 per cent) in this series. There were 4 men and 3 women. The age of these patients was above the average for the group as a whole with 1 in the fourth decade, 2 in the sixth, 1 in the seventh, and 3 in the eighth.

Case C-25.—A 74-year-old Negro man was admitted to the hospital for a herniorrhaphy. The day before his scheduled operation he suddenly developed weakness while at stool. He became very ill with tachycardia, shock, hemoptysis, and a pleural friction rub. A peripheral site of venous thrombosis was never demonstrated. The patient recovered with symptomatic treatment and subsequently had his herniorrhaphy without complication.

Case C-48.—A 64-year-old Negro man was awakened from sleep with pain and tenderness in the right ankle, chills, and fever and shortly thereafter developed pleuritic pain in the left chest accompanied by hemoptysis. Low-grade fever was present but edema was absent. A diagnosis was made of phlebothrombosis in the right leg with pulmonary embolism. Treatment consisted of penicillin and bed rest. Recovery ensued although vein ligation, which is our policy, was not performed.

CASE O-7.—A 73-year-old white man developed soreness in the right calf. A week later he experienced a sudden attack of severe pain in the chest, and dyspnea. Oxygen was required. A month later a similar embolic episode occurred. Three weeks later considerable edema of the left leg developed. Four days prior to referral to us signs of upper internal saphenous phlebitis developed with tenderness to the groin. An inferior vena caval ligation and right lumbar sympathectomy were performed with no subsequent difficulty.

CASE O-26.—A 56-year-old white man developed pain, tenderness, and moderate edema of the left leg two weeks prior to admission. On the tenth and fifth days prior to admission he had two definite episodes suggestive of pulmonary embolism. Ligation of the left superficial femoral and profunda femoris veins was performed. No clot was found at this level. Heparin and Dicumarol therapy was begun. Another pulmonary embolus occurred, and gross hematuria developed. Anticoagulant therapy was discontinued. Signs of phlebothrombosis appeared in the right leg. Vein ligation on the right side was recommended but refused. Recovery occurred. Bilateral superficial femoral vein ligation or inferior vena caval ligation should have been performed initially.

CASE C-39.—A 74-year-old white woman, two months prior to admission, suddenly developed severe cough and dyspnea. She remained in bed for a few days and then resumed activity. Two days later a severe pain in the chest occurred, accompanied by extreme dyspnea. Two weeks prior to admission she developed pain and swelling in the left leg. This frank thrombophlebitis was treated successfully by repeated lumbar sympathetic blocks, elastic support, and early ambulation. We believe that, because of the danger of recurrent embolism, vein ligation should also have been performed.

CASE O-6.—A 52-year-old white man developed mild pain and moderate edema of the right leg with tenderness in the calf. The symptoms developed insidiously. The process in the leg progressed slowly in spite of two lumbar sympathetic blocks and heparinization. One morning as he got out of bed he suddenly became quite dyspneic. This was aggravated when he bathed. He developed a slight cough, but all other signs and symptoms were absent. The history of acute respiratory distress was so definite it was thought that a small pulmonary embolism had occurred. The right common femoral vein was explored and a clot was found extending into the iliac vessels. A vena caval ligation was performed. The patient recovered without further incident.

CASE C-20.—A 38-year-old Negro woman was admitted with a 3 days' history of painful swelling of the right leg, high fever, and chills. Shortly after admission pain in the left chest occurred and the patient began to stutter for the first time in her life. The patient's condition was critical, with tachycardia, rectal temperature of 106° F. and a hot, swollen, nontender right leg. A blood culture was positive for (1) *Staphylococcus albus saprophyticus* and (2) aerobic gram-positive rods. A mild leucocytosis was present and the spinal fluid was clear with normal pressure and normal glucose and chloride concentrations. That evening an episode of sudden, severe pain in the right lower chest, and extreme dyspnea developed. Râles were present at both bases. The patient's condition was desperate. A right superficial femoral vein ligation was performed. No clot was found at that level. Gangrene of the distal end of the right foot developed due to intense arteriolar spasm. No further embolic episodes occurred but the patient became steadily weaker and died of respiratory failure two days after admission. Autopsy was not performed. This appears to be a case of suppurative thrombophlebitis in which vein ligation was performed too late.

Vein interruption was performed in 15 patients. In 4 cases in which pulmonary embolism had occurred, unilateral superficial femoral vein ligation was done in 2 and inferior vena caval ligation in 2. As mentioned previously, 1 of the former died, probably from septic emboli occurring prior to ligation.

In the second, additional emboli occurred following unilateral femoral vein ligation but recovery ensued. This emphasizes the necessity of performing either bilateral superficial femoral ligation or inferior vena caval ligation promptly.

Bilateral superficial femoral vein ligation was performed in 3 of 4 cases of phlebothrombosis without pulmonary embolism, and unilateral common femoral vein ligation in one. Ligation of the internal saphenous vein at its junction with the common femoral vein was performed 5 times (in one instance combined with the common femoral vein ligation previously mentioned) for extensive thrombosis of the internal saphenous vein. In one case of plegmasia cerulea dolens[6] a bilateral superficial femoral vein ligation revealed a loose red clot in the affected leg. Two cases of deep nonsuppurative thrombophlebitis were treated by ligation, one by bilateral, and the other by unilateral, superficial femoral vein ligation. Because in this condition the clot is firmly attached to the vein wall and pulmonary embolism is unlikely, it is questionable that vein ligation in these two cases was necessary.

Follow-up results were obtained in 54 cases from 3 months to 9 years after observation, with an average follow-up period of 31.2 months. The results are presented in Table IV. Good results were obtained in 78 per cent of the cases (Fig. 10). As would be expected the best results occurred in cases of superficial phlebitis, and the poorest results in cases of combined superficial and deep thrombophlebitis.

TABLE IV. RESULTS OF TREATMENT

	SUPERFICIAL PHLEBITIS	DEEP PHLEBITIS	COMBINED PHLEBITIS	ALL CASES
Asymptomatic	4	16	3	23
Mild symptoms	4	13	2	19
Moderate symptoms	–	2	1	3
Severe symptoms	1	4	3	8
Dead		1		1

An analysis of the patients who have had persistence of moderate or severe symptoms indicates that this type of unsatisfactory result occurred in 10 (30 per cent) of 36 charity patients and in only 1 (6 per cent) of 18 private patients. In the one case of superficial phlebitis in which persistent symptoms occurred, these were due to a deep phlebitis which occurred at a later date. Six of eleven individuals with unsatisfactory results were victims of recurrent attacks of phlebitis. It is apparent that the economic status of the patient, and the occurrence of recurrent phlebitis are significant factors in prognosis.

DISCUSSION

Because of the more frequent occurrence of venous thrombosis secondary to infection, trauma, cardiovascular disorders, or other primary precipitating conditions, the study of venous thrombosis as a secondary phenomenon has been the primary concern of investigators. Observations of the condition occurring as a primary phenomenon have been largely limited to special varieties such as superficial recurrent thrombophlebitis migrans. By means of an inclusive

study of all types of spontaneous, or idiopathic thrombophlebitis, it was thought that a clearer picture of the malady might be obtained, and a concept of venous thrombosis as a disease entity rather than a complication might be formulated.

The relative incidence of primary thrombophlebitis is difficult to determine. Few studies have been published and such statistics as are available show widely divergent figures, apparently due to unavoidable variation in clinical material. Fifty-five cases in the present study occurred at Charity Hospital among 1,223 total cases of acute thromboembolism. This is an incidence of 4.5 per cent. The Charity Hospital serves as a larger general hospital in which distant referrals of this type of condition are rare. In a study of 92 consecutive cases of thrombophlebitis of the lower extremities at the University of Minnesota Hospitals, Felder[8] found 9 patients (10 per cent) in whom the deep thrombophlebitis was the primary disease. Miller and Rogers[18] in a report from the Massachusetts General Hospital in 1929 found 36 (17.5 per cent) spontaneous cases among 206 consecutive patients with phlebitis.

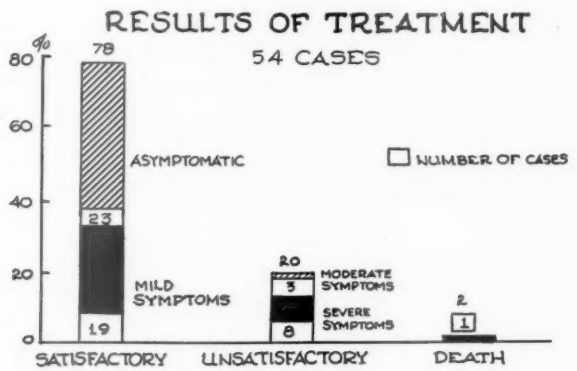

Fig. 10.—Results of treatment in 54 cases of spontaneous thrombophlebitis followed an average of 31.2 months.

Kleinsasser,[15] reporting 502 cases of thrombophlebitis in Army personnel found that 136 (27.1 per cent) were spontaneous. This high figure is undoubtedly largely due to the fairly young type of patient, in whom the common precipitating factors of secondary thrombosis are relatively uncommon.

The spontaneous forms of the disease closely resemble similar types of secondary phlebitis. Superficial or deep veins may be involved. An inflammatory type of thrombophlebitis or, less commonly, phlebothrombosis may occur. Interest has centered largely about idiopathic recurrent thrombophlebitis. The older authors such as Paget,[22] Prescott, Hewett, and others[3] associated the condition with gout. Briggs[3] clearly defined the condition and emphasized its idiopathic nature. He reported 3 new cases and collected 4 from the literature and recommended vein ligation as the therapeutic measure of choice. In 1909, Leo Buerger[4] reported 9 cases of recurrent superficial phlebitis associated with thromboangiitis obliterans in which the pathology of the venous condition closely resembled that in the arteries. He emphasized that symptoms of phlebitis might precede symptoms of arterial disease and stressed the necessity of suspecting

thromboangiitis in any case of recurrent superficial phlebitis. D'Abreu[1] reported a case in which recurrent attacks of phlebitis occurred for 40 years before severe arterial disease developed and led to thigh amputation and death. Edwards[7] reported 3 cases in which phlebitis preceded angiitis and 3 cases in which phlebitis and angiitis occurred together. He stated that at least one-fourth of patients with thromboangiitis obliterans show phlebitis early. Some authors have gone so far as to suggest that thromboangiitis always accompanies, or follows, recurrent superficial phlebitis.[9, 14] It was our expectation to find a number of cases in which thromboangiitis subsequently developed. With perhaps one exception no related arterial disease was present in this series, and in no instance did the expected thromboangiitis subsequently develop. Of course, all cases presenting themselves initially with Buerger's disease were excluded from the study. The age and sex distribution of the cases follow that of phlebitis and not that of thromboangiitis. Buerger[5] recognized the occurrence of recurrent superficial thrombophlebitis in the absence of thromboangiitis obliterans. Barker[2] reported 40 cases of recurrent idiopathic thrombophlebitis and 39 cases of idiopathic thrombophlebitis occurring in single episodes. In none of these was an associated thromboangiitis present. Although thromboangiitis obliterans must be suspected and carefully looked for in all cases of recurrent phlebitis, particularly those occurring in young men, there are many cases of spontaneous phlebitis of all types which bear no apparent relation to any other vascular disease.

As Barker[2] pointed out, the clinical picture in the cases of deep vein involvement in no way differs from that seen in cases of secondary phlebitis. The majority of cases manifest themselves as a nonsuppurative thrombophlebitis. In this group pulmonary embolism is rare. However, as Homans[13] emphasized, spontaneous silent phlebothrombosis with embolism occurs not infrequently and may be confused with coronary disease. He reported 11 such cases. Manson-Bahr and Chambers[16] reported 627 cases of thrombophlebitis occurring in epidemic form in the East Africa Command of the British Army. Because the epidemic occurred chiefly in patients treated in two venereal treatment centers, he suggested a viral etiology with transmission by venipuncture or other means.

The frequency of pulmonary embolism varies widely depending on the type of peripheral venous thrombosis. In general the frequency of embolism is low, and fatality due to embolism even lower as the process is usually of the nonsuppurative thrombophlebitic type in which emboli are relatively uncommon and usually small. The incidence in our series was 7.7 per cent. In these seven cases embolism occurred as a primary episode in 2, as a complication of evident phlebothrombosis in 2, and in another patient was associated with thrombophlebitis of one leg and phlebothrombosis in the other. A small embolus complicated one case of iliofemoral thrombophlebitis and in the one fatal case emboli originated in a suppurative thrombophlebitis of the right lower extremity.

Some observers have reported a surprisingly high incidence of pulmonary embolism in patients with recurrent thrombophlebitis migrans. In Daguillon's[3] series of 12 cases of recurrent phlebitis, pulmonary embolism occurred in 6 and was the cause of death in 3. In Barker's[2] series of 40 cases of recurrent idiopathic thrombophlebitis, acute infarction of the lung occurred in 12, with fatalities in 2. These occurred primarily in cases with deep vein involvement. In the 40 cases, 73 attacks of superficial phlebitis occurred and 19 episodes of deep phlebitis. Of the 17 acute infarctions of the lung occurring in 12 patients, 11 were associated with deep phlebitis and 5 with involvement of the superficial veins. On the other hand, among 39 patients with a single episode of idiopathic phlebitis, nonfatal pulmonary infarction occurred in only 3. Fischer[10] reported involvement of the lungs in 23 of 114 collected cases of thrombophlebitis migrans, of which 5 ended fatally.

Spontaneous phlebothrombosis with pulmonary embolism is a significant problem. Not infrequently the embolism will occur as the primary manifestation. This occurred in 2 of 5 such cases in our series. Homans[13] reported 11 cases, and McCutcheon and Cantey[17] reported 2.

Although no clear-cut cases of involvement of other visceral blood vessels occurred in this series, the not infrequent involvement of such veins has been reported, particularly in association with recurrent superficial thrombophlebitis. In Fischer's[10] 6 cases of thrombophlebitis migrans, involvement of the visceral veins occurred in 4. In the series of 114 cases he collected from the literature, visceral involvement occurred in 9, the mesenteric veins being involved in 5, the heart in 2, and the brain in 2. Gerber and Mendlowitz[11] reported 6 fatal cases of visceral thrombophlebitis migrans occurring at the New York Mount Sinai Hospital over a twelve-year period. Moorehead and Abrahamson[19] reported visceral involvement in 3 of 4 reported cases of thromboangiitis obliterans. This is a grave form of the disease and the mortality is high. It seems to represent an entirely different type of disease.

Although many suggestions have been made as to the etiology of spontaneous phlebitis, it must be admitted that nothing of definite etiological significance has been established. The early authors suggested gout.[22] Briggs[5] suggested the possible importance of sclerotic changes in the walls of the veins. Bacterial infection is unlikely as cultures of the veins have been uniformly negative.[2, 10] It did apparently occur in our one fatal case. Three of the 6 fatal cases of visceral phlebitis reported by Gerber and Mendlowitz[11] had an associated thrombocytopenia. Harkavy[12] considered sensitiveness to tobacco as an important etiological factor. In Manson-Bahr and Chamber's[16] report of epidemic thrombophlebitis in the East Africa Command, a viral etiology is suggested. The epidemic character of the disease reported by them is unique.

CONCLUSIONS

Venous thrombosis, in all its forms, may occur spontaneously. In this study, spontaneous thrombophlebitis represented 4.5 per cent of 1,223 cases of venous thrombosis. The clinical picture closely resembles similar types of

phlebitis occurring secondary to some other condition. In spontaneous cases there is a relatively high incidence of involvement of the right lower extremity, of superficial phlebitis, and of recurrence.

Thromboembolic disease of the venous system is protean in its manifestations, but the clinical picture is similar whether the disease occurs as a primary phenomenon or following some traumatic episode. For this reason, it should be considered as a disease entity and not merely as a complicating feature of other disorders.

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THE EFFECT OF VENOUS OCCLUSION ON ARTERIAL BLOOD FLOW IN THE EXTREMITIES

An Experimental Study

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In 1936, Collens and Wilensky[7] introduced intermittent venous occlusion for the treatment of patients with obliterative vascular disease and reported beneficial results in a high percentage of their cases. Since then many others[2, 5, 6, 8, 11, 18] have studied the clinical effects of intermittent venous occlusion in man, but opinion as to its efficacy has varied widely.

Two types of vascular change are said to result from intermittent venous occlusion: (1) the acute effects, which include the changes occurring during the period of occlusion and immediately following its release; and (2) the chronic effects, which may include the changes occurring in the collateral circulation to the limb over a long period. The acute effects have been investigated in man and animals with conflicting results. The chronic effects have been observed only in patients with obliterative vascular disease, again with conflicting results, and have not been subjected to direct experiment.

Methods used for examining the acute effects of intermittent venous occlusion on arterial blood flow are of two types: (1) the first has been designed to study the circulation in man by various indirect methods when venous occlusion is applied for a limited time; and (2) the second has been designed to study the circulation in laboratory animals by measuring the arterial blood flow directly, during and after short periods of venous occlusion.

The indirect methods used include surface temperature determinations, blood-oxygen changes, plethysmography, and capillary microscopy.[1, 3, 12, 14, 24] The evidence from these sources suggests that in man there is no increase in mean arterial blood flow during venous occlusion.

In 1941, Linton and co-workers[17] reported the results of their study of arterial flow during venous occlusion in dogs, using a thermostromuhr method. Venous occlusion was produced either by a pneumatic cuff or by clamping the major veins. These investigators reported that during venous occlusion the arterial inflow to the hind limb increased, and immediately after release of the occlusion the arterial flow decreased. On the basis of this result Linton recommended that the period of occlusion be longer than the period of release when intermittent venous occlusion was to be used for therapy in man. Gregg,

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Pritchard, and Shipley,[13] in 1948, reinvestigated the results of Linton and co-workers in dogs. They used three different types of instruments to measure arterial blood flow in the dog's hind leg: (1) a Baldes-Herrick thermostromuhr, (2) an orifice meter, and (3) an optically-recording rotameter. With the thermostromuhr they obtained the same results as Linton—i.e., an apparent increase in arterial flow during venous occlusion, and an apparent decrease following its release. With the other two methods they consistently found a decrease in arterial flow during venous occlusion and an increase on release.

Tests by Gregg and associates have revealed serious inaccuracies in the Baldes-Herrick thermostromuhr method of measuring blood flow, since many factors other than blood flow influence the results significantly. "The amount of backflow in the flow pattern is particularly important since the flow pattern in most arteries either normally contains backflow or it can be induced, and the instrument is so sensitive that such a change can cause the device to indicate incorrectly the directional change in flow." Since the rotameter and orifice meter are not subject to the same criticisms, Gregg and associates concluded that the results obtained with the thermostromuhr during venous occlusion were diametrically opposed to the true state of affairs. They stated therefore that the arterial blood flow decreases during venous occlusion and increases after release of the occlusion.

METHODS

In the study reported here we have investigated the acute effects of venous occlusion on the rate of arterial blood flow in animals by two direct methods not previously used for this purpose.

Cats weighing 1.8 to 3.5 kilograms were anesthetized with chloralose, 70 mg. per kilogram of body weight, or with Nembutal, 30 mg. per kilogram of body weight. In some experiments the hind limbs were sympathectomized either before or during perfusion. In the first method (Fig. 1) the hind leg was perfused through the external iliac or femoral artery or aorta. The rate of blood flow and perfusion pressure were both measured directly. A carotid artery, or a carotid and a brachial artery, were cannulated, and blood taken into the perfusion pump. The blood, kept at 37° C. by a hot-water jacket, was pumped into the leg and returned by normal venous channels. The rate of blood flow was recorded by a volume recorder and registered on a kymograph drum. It is important to emphasize that the actual volume of blood entering the leg was measured, so that the errors associated with indirect methods were eliminated. Reference has previously been made to the method[23] and full details are being published elsewhere by one of us (J. R. V.).

In the second method, serial radiographs were taken at intervals of 0.5 to 1.5 seconds after the injection of Thorotrast into the abdominal aorta through a Polythene tube tied into the stump of the inferior mesenteric artery.

Venous occlusion was done with a pneumatic cuff inflated to known pressures measured with a mercury manometer.

RESULTS

The effect of venous occlusion on the rate of arterial blood flow in the perfused leg was studied in 12 cats.

At fixed cuff pressures of 20 to 80 mm. Hg (27 observations), 80 to 100 mm. Hg (11 observations), and 100 to 200 mm. Hg (17 observations) for two or three minutes, the arterial inflow always decreased. Fig. 2 is a typical experiment, in which the blood flow was reduced 18.7 per cent during a two-minute period of occlusion. Even at very low occlusion pressures the flow was decreased. For example, with a pressure of 30 mm. Hg the flow was reduced

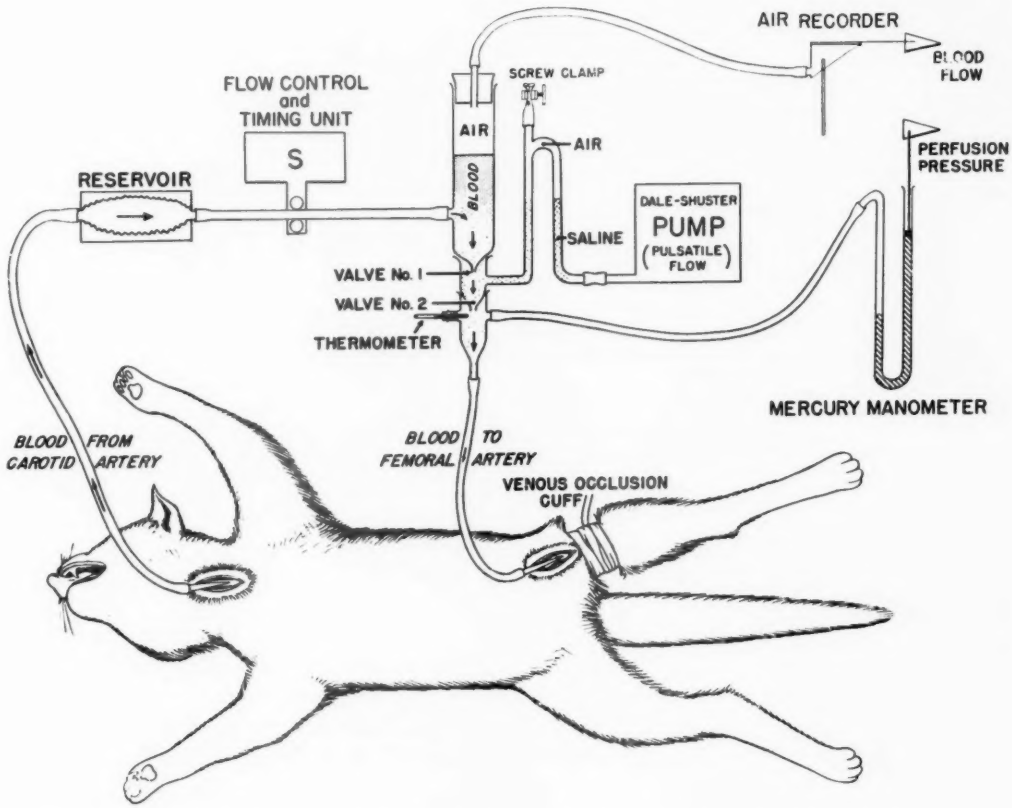

Fig. 1.—Simplified diagram of the perfusion method used. Consult text for details.

10 to 20 per cent, and with an occlusion pressure of 40 mm. Hg the flow was reduced 10 to 30 per cent. Sometimes immediately after release of the pressure, reactive hyperemia was observed, but this never lasted longer than twenty to thirty seconds, and in no instance compensated for the reduced flow during occlusion. The reactive hyperemia, when present, was followed by a reduction in blood flow to the rate before occlusion or, as in several experiments, even further (Fig. 2).

To study further the effects of venous occlusion, individual veins were clamped with bulldog clamps. The arterial inflow decreased in all of the twenty-one instances where the vena cava, the common iliac, the external iliac,

or the femoral vein was clamped. Fig. 3 is an example which shows that during the three-minute period of clamping the external iliac vein, the arterial flow was reduced 21 per cent.

Since blood flow was found to decrease during the period of occlusion, if any over-all increase in flow was to be obtained, then it must be through reactive hyperemia following release of the occlusion. A cycle with the cuff inflated for 30 seconds and deflated for 30 seconds was therefore adopted. In nine experiments under these conditions an over-all increase in flow was never observed. The reactive hyperemia in no instance compensated for the decreased

EFFECT OF VENOUS OCCLUSION
ON ARTERIAL BLOOD FLOW

MEAN PERFUSION PRESSURE — 160 mm. Hg
VENOUS OCCLUSION PRESSURE — 80 mm. Hg

BEFORE OCCLUSION	DURING OCCLUSION		AFTER OCCLUSION
cc./Min.	cc./Min.	% Decrease	cc./Min.
32	26	18.7 %	28

Fig. 2.—Results of an experiment on a 1.9 kilogram cat with bilateral lumbar sympathectomy. Both hind limbs perfused from bifurcation of aorta. The flow during a two-minute period of occlusion was markedly diminished and after release of the occlusion did not quite return to the control level.

EFFECT OF VENOUS OCCLUSION
ON ARTERIAL BLOOD FLOW

MEAN PERFUSION PRESSURE — 165 mm. Hg
Occlusion by Clamping External Iliac Vein

BEFORE OCCLUSION	DURING OCCLUSION		AFTER OCCLUSION
cc./Min.	cc./Min.	% Decrease	cc./Min.
19	15	21 %	18

Fig. 3.—Results of an experiment on a 2.6 kilogram cat with right hind limb perfusion. The flow during a three-minute period of clamping the external iliac vein was markedly reduced.

blood flow during occlusion; although reduced blood flow was observed on all occasions, no reactive hyperemia followed occlusions at the lower pressures. The rate of blood flow after intermittent venous occlusion was never greater than the rate before; in some instances it was less than the control level. In all these occlusions, section of the sympathetic, sciatic, or femoral nerves did not alter the results. Fig. 4 is illustrative of a typical experiment.

To study the circulation visually during venous occlusion, and to confirm the results obtained on the perfused limbs, serial radiographs were taken of both hind legs, one of which was occluded with the cuff for two minutes before the injection of Thorotrast. In each of the five cats studied the radiographs showed that filling of the vessels below the cuff on the occluded leg was much

delayed compared with the control leg. There was also a considerable decrease in the number of small arterial vessels seen under the occluding cuff, and there was compression of the soft tissues.

CONCOMITANT VENOUS AND ARTERIAL LIGATION

As a result of observations made during the Boer War and World War I, Makins[19] came to the conclusion that in patients whose major arteries had to be ligated because of injury, the incidence of gangrene was less if the accompanying vein was also divided. This form of therapeutic venous occlusion has been investigated extensively since its introduction, and the results are conflicting.[4, 9, 15, 20-22, 25] DeBakey and Simeone,[10] in 1946, after analyzing the data on battle injuries of the arteries in American wounded men in World War II, and after a comprehensive and critical review of the literature, stated: "The conclusion seems legitimate, on the basis of Makins' figures for World War I and the American figures for World War II, that ligation of the concomitant vein furnishes no protection whatsoever against the development of gangrene after acute arterial occlusion and ligation in battle casualties."

EFFECT OF VENOUS OCCLUSION
ON ARTERIAL BLOOD FLOW

MEAN PERFUSION PRESSURE — 135 mm. Hg
VENOUS OCCLUSION PRESSURE — 60 mm. Hg

BEFORE OCCLUSION	DURING OCCLUSION		AFTER OCCLUSION
cc. / Min.	cc. / Min.	% Decrease	cc. / Min.
18	12	33 %	16

AV. FLOW DURING I.V.O. (on + off) — 14.5 cc. or 19.4% DECREASE

Fig. 4.—Results of an experiment on a 2.6 kilogram cat with right hind limb perfusion. Venous occlusion was applied for six minutes in a cycle of thirty seconds' occlusion and thirty seconds' release. During the period of occlusion the flow was reduced 33 per cent. The average flow over the entire period of intermittent venous occlusion (occlusion plus release) was 19.4 per cent less than the control flow.

With our technique, when the femoral or iliac artery was clamped there was a marked reduction in the blood flow to the limb. When the concomitant vein was then clamped, we did not in any instance observe an increase in arterial blood flow. We did no survival experiments to test the incidence of gangrene under such conditions. On the basis of results from the literature and from our own observations, the majority of the evidence fails to substantiate the view that simultaneous vein ligation after arterial interruption causes an increased blood flow to an extremity.

DISCUSSION

The hypothesis that intermittent venous occlusion promotes the development of collateral circulation has been based on two alleged effects during and immediately after release of occlusion: (1) an increase in arterial inflow during the period of occlusion,[17] and (2) a reactive hyperemia following release of the occlusion, a concept based on the work of Lewis and Grant[16] and put forward

by Collens and Wilensky.[7] The final proof of the effect of reactive hyperemia rests on the demonstration of increased circulation to an extremity after prolonged intermittent venous occlusion over weeks.

As regards the increase in arterial inflow during venous occlusion, it is clear, from the data presented here and by Gregg and co-workers,[13] that arterial inflow considerably decreases during the period of occlusion. It seems logical that venous occlusion by a cuff should lead to a decrease in arterial flow: (1) as was pointed out by Halperin and associates[14] the pressure gradient decreases from the arterial to the venous side because of the increased venous pressure; and (2) the caliber of the vascular bed under the cuff decreases, with an increased resistance and an accompanying retardation of flow. This is demonstrated directly in our radiographs. The pressure drop across arterioles is usually about 40 mm. Hg; hence at their peripheral end the mean pressure is only some 30 mm. Hg. It is clear, therefore, that even very low occlusion pressures, far below the diastolic level, will obliterate small arterioles under the cuff, though leaving the main arteries comparatively unaffected. It is conceivable that such an effect might be exaggerated in a patient with obliterative vascular disease whose main blood supply was through relatively low pressure collaterals.

It is well known that the higher the level of the occluding pressure, the greater will be the reactive hyperemia upon release. In our experiments the compensatory hyperemia did not repay the debt incurred during the period of occlusion. It lasted only twenty to thirty seconds, and the subsequent rate of flow was either the same as the preocclusion rate or lower; it was never higher. It thus appears from the results of experiments on the acute effects of venous occlusion that there is a decrease in supply of blood to the extremity during occlusion and no persistent increase after its release. Whether repeated venous occlusion over a long period increases collateral circulation has not been proved; no alternate case reports have been published, and the experimental data are lacking altogether.

SUMMARY

1. The acute effects of venous occlusion on the rate of arterial inflow to the hind limbs of cats have been studied directly by perfusion and by serial radiography.

2. During venous occlusion the arterial inflow to the extremity decreases.

3. After release of the occlusion, there is commonly a transient increase in arterial flow above the preocclusion level, but this reactive hyperemia does not compensate for the decreased flow during occlusion. The rate of flow following release is equal to, or less than, the rate preceding occlusion—never higher.

4. Serial radiography showed a delay in the filling of the vessels on the occluded side, and a considerable reduction in the number of visible small arterial vessels under the inflated cuff.

5. Concomitant clamping of the accompanying vein fails to cause an increase in arterial blood flow to the limb when the major artery has been clamped.

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OBSERVATIONS ON THE DIRECT EFFECT OF COLD ON BLOOD VESSELS IN THE HUMAN EXTREMITY AND ITS RELATION TO PERIPHERAL VASCULAR DISEASE

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A SYMPATHECTOMIZED extremity usually remains warmer than one with normal vasomotor activity when a patient is exposed to a moderately cool environment. Under certain conditions vasoconstriction will occur even in sympathectomized extremities.[5, 12, 14] This has been attributed to various factors. Lewis and Landis[14] showed that vasoconstriction could be produced by local cooling of extremities affected by Raynaud's disease after sympathectomy or nerve block and indicated that this was probably due to an increased sensitivity of the vessels to cold caused by the disease. Lewis and Pickering[15] demonstrated that when the body is warmed, with the hands initially at different temperatures, the onset of vasodilatation is delayed in the cool hand, and attributed this to the local constrictor action of cold on the arteries and arterioles. Pickering and Hess[17] made similar observations on the feet and individual digits. Cannon[3] suggested that the smooth muscle of the arteriole might become sensitized to cold as the result of denervation. Many investigators[6, 7, 9, 11, 19] have demonstrated an increased sensitivity of vessels to epinephrine or other vasoconstrictor substances[11] following sympathectomy. Most of these indicated that sensitization was greater following postganglionic sympathectomy than after preganglionic sympathectomy. Ascroft[1] concluded from studies on monkeys that the reaction to adrenalin was three times as great in a limb after preganglionic sympathectomy as in a normal limb, and ten times normal after ganglionectomy. Freeman, from experiments on man[8] and animals,[10] postulated that the blood flow in a sympathectomized extremity is determined by tissue metabolism, within certain limits of temperature. Doupe[5] observed the effect of local cooling on denervated vessels and reported that vessels become more sensitive to cold after postganglionic sympathectomy than after preganglionic sympathectomy. This was suggested as the reason a completely denervated extremity tends to remain cold while an extremity with a preganglionic sympathectomy is usually warm. Perkins and associates[16] demonstrated that the vasoconstriction which took place in the denervated and sympathectomized paws of cats on exposure to cold was a local reaction and presented evidence to support their impression that it was

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due (1) to the local action of cold on the smooth muscle of the arteriole and (2) to reduced formation of vasodilator metabolites from cooling of the tissue, as described by Freeman.

Our interest in this problem has been aroused by several patients with obliterative arterial disease, either arteriosclerosis or thrombo-angiitis obliterans, who complained that, despite sympathectomy, their feet became "cold" on exposure to moderate temperatures. This would, of course, occur in any extremity in which the blood flow was so impaired that it could not replace the heat loss, even when fully vasodilated. However, examination of two of these

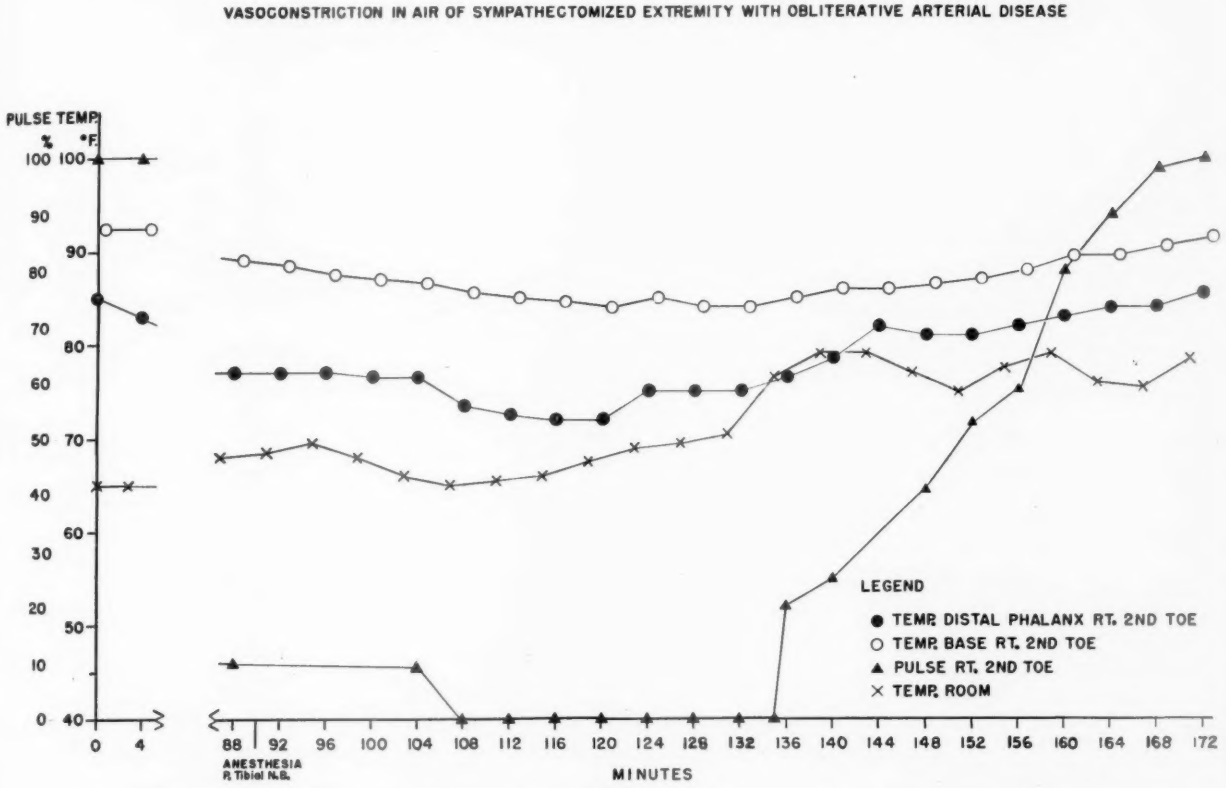

Fig. 1.—Illustrates the disappearance of recordable pulsations in the second toe of a sympathectomized extremity with advanced obliterative arterial disease (arteriosclerosis) after 108 minutes at an ambient temperature of 65° F. to 70° F. in a controlled temperature room. The amplitude of pulsations on admission to the room was taken as 100 per cent. Pulsations did not return within 45 minutes after anesthesia over the posterior tibial nerve distribution (10 minutes after block). The room temperature was gradually increased. When the temperature of the room and toe reached 77° F., the pulsations returned and rapidly increased in size.

sympathectomized extremities in the laboratory showed that digital pulsations actually disappeared after 1½ to 2 hours in the controlled temperature room at 65° to 70° F. There was no increase in temperature or return of pulsations after anesthetization of the posterior tibial nerve as would be anticipated had the result been due to sympathetic activity. Completeness of the sympathectomies was further confirmed by the absence of sweating over the feet and lower legs as tested by a Richter neurodermometer. The following graph (Fig. 1) illustrates one of these cases.

It can be seen that digital pulsations, recorded from the second toe by the Grass Electroplethysmograph,* disappeared after 1 hour and 48 minutes in the controlled temperature room and did not return within 45 minutes after anesthesia over the posterior tibial nerve distribution. The room temperature was gradually increased. When the temperature of the room and toe reached 77° F., the pulsations rapidly returned to their original size.

Since the vasoconstriction in this case could easily be explained if sympathetic activity were present, and since the return of pulsations occurred after increasing the room temperature to a point where reflex vasodilatation might possibly take place, the patient was recalled and rechecked for evidence of sympathetic activity. Again no sweating could be detected, and no increase in temperature or size of pulsations occurred after posterior tibial nerve block.

The problem arose as to the relative importance of the factors previously discussed in producing the vasoconstriction in these cases. We wondered at what temperature the "direct effect" of cold on blood vessels might occur in human extremities and how much this differed in individuals, particularly those with varying degrees of obliterative arterial disease.

This portion of the study has been confined to sympathectomized lower extremities so that only the preganglionic type of sympathectomy would be included. Variations in reaction to cold due to type of sympathectomy, as discussed by Doupe, should thereby be eliminated.

SUBJECTS

Table I lists the twenty-six sympathectomized lower extremities discussed in this paper with relevant information about each. Ten additional studies had been made at the time of this report with similar results. The designations, 0 to +++, give our estimate of the severity of obliterative disease based on complete laboratory studies including digital pulsations, palpation of peripheral pulses, oscillometry, a walking test, and ergometry. Only those cases were studied which showed no evidence of sympathetic activity when tested as follows:

The patient was heated for one hour under an electric blanket sufficiently warm to produce profuse sweating of normally innervated areas of the body. The sympathectomized extremity was then tested for sudomotor activity using a Richter neurodermometer. If no sweating could be detected below the tibial tubercle of the sympathectomized extremity, the patient, clad only in shorts or a light slip, was exposed to a temperature of 68° F. for one hour in a controlled temperature room. If the temperature of the great toe fell below 90° F. during this hour of cooling, or, if the amplitude of the pulsations of the second toe, recorded by the Grass Electroplethysmograph, showed any decrease in size, the tibial nerve was anesthetized at the ankle using 2 per cent procaine. Any rise in skin temperature or increase in amplitude of digital pulsations following this procedure was considered evidence of sympathetic activity.

METHOD

Water was selected as the cooling medium because it allowed more rapid and more even transfer of heat than would have been possible with air. A plastic cylinder, 14 inches high and 5 inches in diameter with an opening near the base large enough to admit the foot and ankle, was used as the container

*Grass Instrument Co., Quincy, Mass.

for the water. A watertight seal was made by cementing a thin rubber diaphragm to the container and around the ankle. In order to permit gradual cooling of the part, the water temperature was lowered slowly by removing water through a drain near the base of the cylinder and adding cooler water from above.

TABLE I. SUBJECTS INCLUDED IN THIS STUDY

PATIENT	AGE (YEARS)	DIAGNOSIS	SEVERITY OF DISEASE	EXTREMITY (TEST NO. ON GRAPHS)	TIME BETWEEN SYMPATHECTOMY AND TEST	GANGLIA REMOVED
J. L.	57	A-S	++	Left (1)	7 Mo.	L_2, L_3, L_4
			++	Right (2)	7 Mo.	D_{12}, L_1, L_2, L_3, L_4
D. D.	54	A-S	++	Left (3)	12 Mo.	L_1, L_2, L_3
J. B.	40	TAO	++	Right (4)	7 Days	L_1, L_2, L_3
H. A.	53	TAO	+++	Left (5)	66 Mo.	L_1, L_2, L_3
			++	Right (16)	78 Mo.	L_1, L_2, L_3
B. C.	55	A-S	++	Left (6)	12 Mo.	L_1, L_2, L_3, L_4
			++	Right (21)	12 Mo.	L_1, L_2, L_3, L_4
A. G.	58	A-S	+++	Left (7)	19 Mo.	L_1, L_2, L_3
F. D.	60	A-S	+++	Right (8)	7 Days	D_{12}, L_1, L_2, L_3, L_4
M. F.	72	A-S	++	Left (9)	14 Mo.	T_{12}, L_1, L_2, L_3, L_4
D. M.	62	A-S	+++	Right (10)	4 Mo.	D_{12}, L_1, L_2, L_3, L_4
J. F.	35	TAO	+	Right (11)	10 Mo.	L_1, L_2, L_3, L_4
			0	Left (22)	10 Mo.	L_1, L_2, L_3, L_4
D. L.	35	Femoral A.V. Aneurysm	0	Left (12)	6 Days	L_1, L_2, L_3, L_4
			0	Left (18)	27 Days	
H. D.	57	A-S	++	Right (13)	18 Mo.	D_{12}, L_1, L_2, L_3, L_4
			+	Left (23)	18 Mo.	L_1, L_2, L_3, L_4
H. S.	55	A-S	++	Left (14)	14 Mo.	D_{12}, L_1, L_2, L_3
R. M.	43	A-S	+	Right (15)	30 Mo.	L_2, L_3
			+	Left (25)	33 Mo.	L_1, L_2, L_3
N. B.	64	A-S	++	Left (17)	14 Mo.	L_1, L_2, L_3
M. A. S.	57	A-S	+++	Left (19)	4 Mo.	D_{12}, L_1, L_2, L_3, L_4, L_5
M. T. S.	39	TAO	++	Right (20)	9 Mo.	L_1, L_2, L_3
H. L.	58	A-S	+	Left (24)	18 Mo.	D_{12}, L_1, L_2, L_3, L_4
C. F.	51	A-S	+++	Right (26)	9 Mo.	L_1, L_3, L_4

Skin temperatures were measured using No. 24 iron-constantan thermocouples applied to the plantar surfaces of the distal phalanx of the great toe, distal phalanx of the second toe, and base of the second toe of each foot by wisps of cotton dipped in collodion. Other thermocouples were used to determine the temperature of the water about the foot being cooled, and the room temperature. These temperatures were recorded by an eight-lead Brown Potentiometer* arranged so that successive leads would record every 30 seconds, thereby requiring 4 minutes for a complete cycle, or, when desired, any particular lead could be made to record every 30 seconds.

Stainless steel plethysmograph cups were applied to each second toe and arranged so that one thermocouple was within the cup and another just outside the cup. Since air was used as the transmission medium for plethysmography, the thermocouple on the distal phalanx of the second toe was surrounded by air, and the one at the base of the toe by water, during the cooling period.

*Brown Instrument Co., Division of Minneapolis-Honeywell Regulator Co., Philadelphia, Pa.

OBSERVATIONS AND DISCUSSION

1. *Variations in Reaction of Vessels of Sympathectomized Extremities to Temperature Changes.*—The following graph (Fig. 2) shows the major decreases in pulsations of the toes as the result of cooling in twenty-five tests on twenty-four different extremities. The average pulse obtained after the subject had been resting in a horizontal position for at least ½ hour, exposed to an ambient temperature of 68° F., was taken as 100 per cent for the purpose of this study. The temperature of the second toe after an hour at 68° F., as represented by the top of the column in each test, gives an indication of the completeness of sympathectomy because in all cases it remained above 84° F. Since in only one case (No. 8) was there any appreciable decrease in pulsations during the

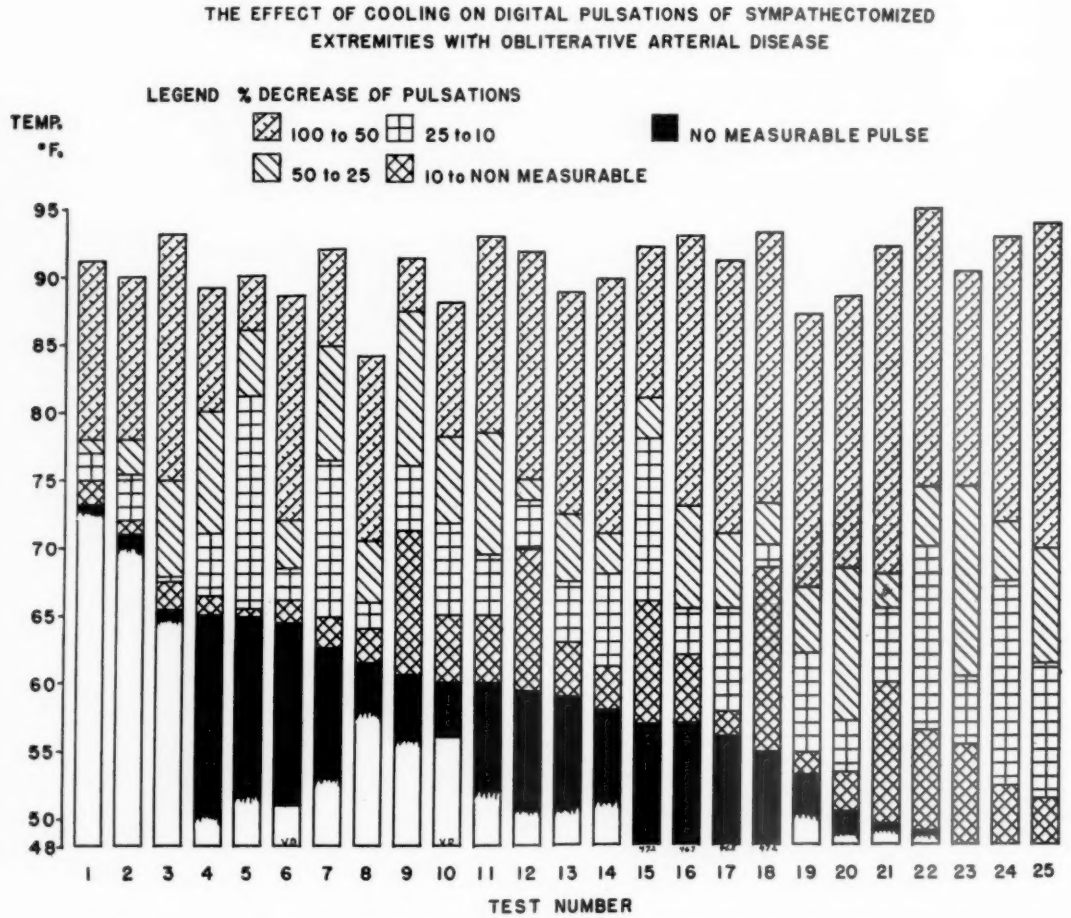

Fig. 2.—Each column represents a test on a sympathectomized extremity and shows the major decreases in amplitude of digital pulsations as the temperature of the toe was progressively lowered. The amplitude of pulsations recorded after the subject had been resting in a horizontal position for at least ½ hour exposed to an ambient temperature of 68°F. was taken as 100 per cent. The top of the column indicates the temperature of the toe after the patient has been exposed to an ambient temperature of 68° F. for 1 hour, before cooling the foot with water. The jagged edge of the last shaded block gives the lowest temperature to which the toe was cooled. Two toes (Nos. 6 and 10) vasodilated while being cooled. The temperature at which vasodilatation occurred is indicated by the straight base of the block. Three extremities (Nos. 23, 24 and 25) still had measurable digital pulsations when the second toes were cooled to 48° F.

hour in the cold room (68° F.), these temperatures also give a rough comparison of blood flows.

The extremities are arranged in order of reaction to cold, those vasoconstricting at the higher temperatures being listed first. The order is based chiefly on the temperature at which the pulsations became indistinct. Blood flow studies using a venous occlusion cuff on the toe just proximal to the plethysmograph cup, or around the ankle,[4] indicated that the blood flow was reduced to at least 10 per cent of its starting value when the pulsations became too small to measure by our method. The temperature range over which major changes in pulsations occurred is designated by blocks showing amplitude of pulsations in per cent of starting pulsations. In making this graph, blocks of 100 to 50 per cent, 50 to 25 per cent, 25 to 10 per cent, and 10 per cent to no measurable pulsations have been used. Not all extremities were cooled to the same temperature. The lowest temperature of the toe reached during cooling is shown as the base of the last block in each test. With the patient in a horizontal position, the amplitude of pulsations appears to be a good index of vasoconstriction and digital blood flow. This is discussed in a previous paper.[4]

Two toes (Nos. 6 and 10) vasodilated as the temperature was progressively lowered following vasoconstriction. In one of these (No. 6) rapid, complete vasodilatation occurred within a few minutes in spite of continued efforts to cool the part. The other alternately vasodilated and constricted. This was sufficient to gradually increase the temperature of the toe while still in water.

In general, extremities with advanced disease vasoconstricted at higher temperatures than those with less impairment of circulation. Several exceptions were apparent, notably test 19. Three patients (H. A., J. F., H. D.) had considerably more arterial insufficiency in one extremity than the other. In each case, the extremity with the more advanced disease vasocontsricted at the higher temperature. One patient (B. C.) had, if anything, slightly more obliterative disease in the right leg; but the left second toe showed much greater reaction to cold than the right second toe. Too few cases of thromboangiitis obliterans were studied to permit comparison with the arteriosclerotic group, but in three out of five cases of the former, the extremities vasoconstricted at relatively high temperatures. Further tests are being made to determine the reaction of vessels to cold following nerve block before sympathectomy and for varying periods after sympathectomy.

It was evident that variations in blood flow alone could not have accounted for the marked differences in surface temperatures of the toes at the time the vessels constricted, because frequently toes with obviously greater blood flow vasoconstricted at higher temperatures than those with less. An attempt was made to reduce this factor by cooling the extremities until the blood flow became very small and then allowing gradual warming until vasodilatation occurred. This procedure appeared satisfactory in nineteen of the twenty-five tests. As mentioned before, two toes vasodilated while still being

cooled. Four others vasodilated so rapidly after draining the water that accurate measurements could not be made. The graph (Fig. 3) illustrates the results in ten representative cases. The variations in reactions to cold are still apparent, although the temperatures at which vasodilatation occurred are sometimes lower than the constriction temperatures. This might be explained by accumulation of vasodilator metabolites or "injury substances."[13, 20] A few changes in order of reaction of the various extremities were noted. Test 16 is an example.

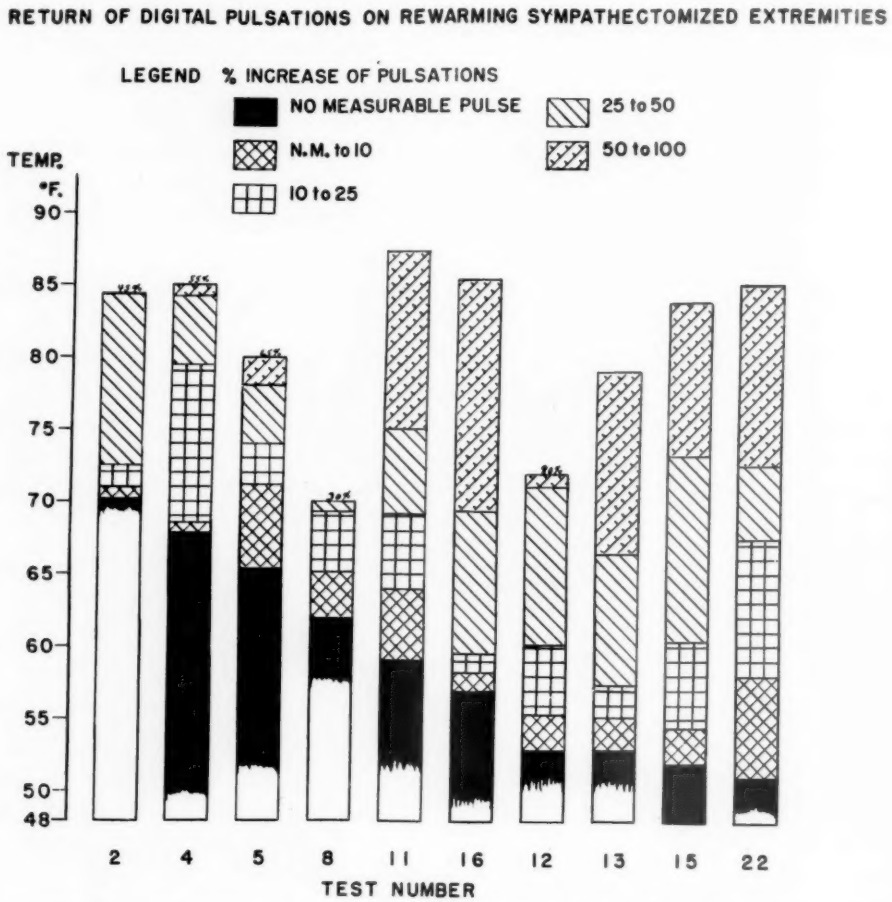

Fig. 3.—Each column represents the return of pulsations in the second toe of the extremity being tested as it was allowed to rewarm following cooling. The lower edge of the last shaded block indicates the lowest temperature of the toe reached during cooling. The per cent increase (return) of pulsations was computed by comparing the amplitude of returning pulsations with what they had been previous to cooling the foot with water as explained in Fig. 2. Certain tests had to be terminated because of lack of time before the pulsations had returned to the original size.

Frequently, as seen in Figs. 4 and 5, the temperature rose much faster at the base of the toe than at the distal phalanx. The average temperature of the toe was approximated by taking the average of these two temperatures. During the cooling period little difficulty was encountered in keeping the proximal end of the toe within a few degrees of the distal phalanx since this could be regulated by increasing or decreasing the rate of cooling.

2. *Evaluation of Factors Involved in Vasoconstriction of the Sympathectomized Extremity.*—Several methods were used in an attempt to evaluate the factors responsible for the vasoconstriction in these extremities on exposure to cold. Fifteen lower extremities of ten patients with bilateral lumbar sympathectomies were studied, using one foot as a control while the other was cooled.

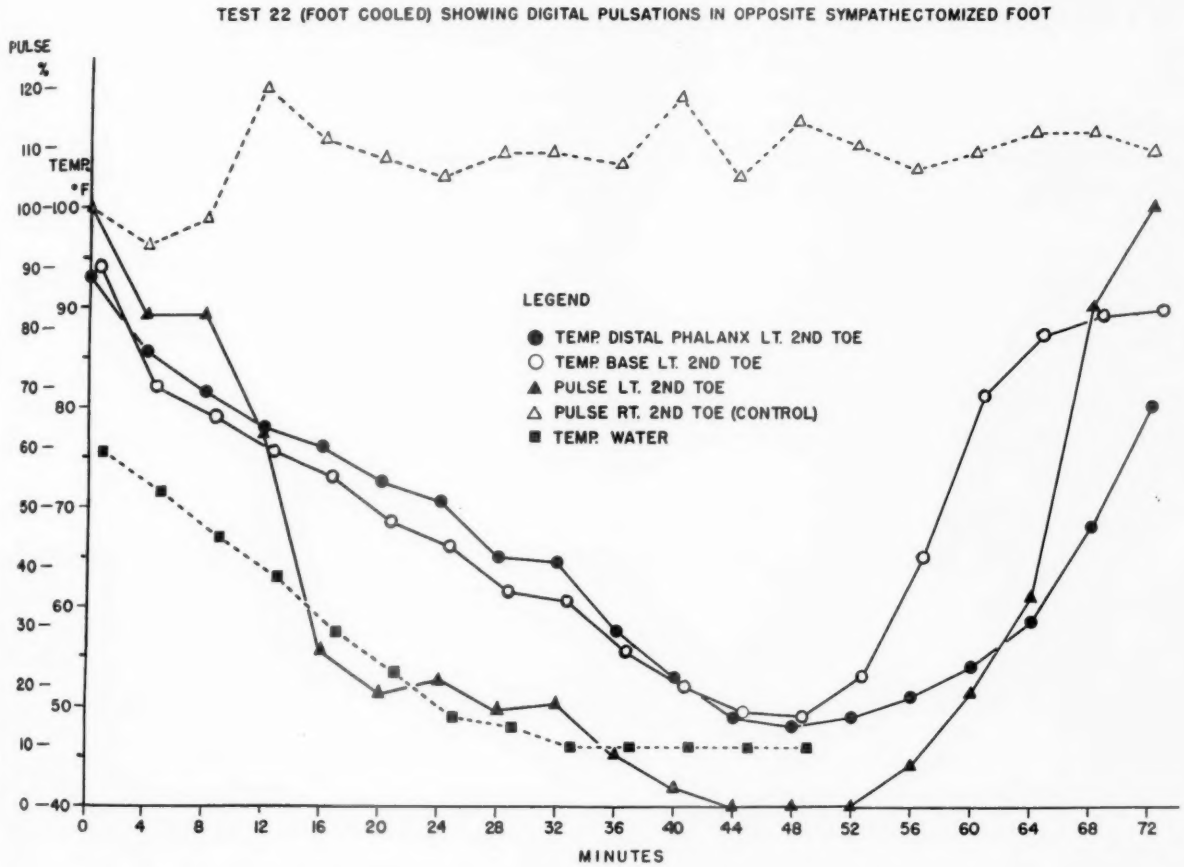

Fig. 4.—This graph records the per cent decrease in amplitude of pulsations of the second toe as the foot was cooled by water. The first water temperature graphed shows the temperature of the water and time at which it was placed in the container about the foot. The last water temperature listed indicates the time at which the water was drained and the foot exposed to room temperature (68° F.). In certain tests the room temperature was increased in order to warm the toe sufficiently to permit vasodilatation. The pulsations recorded from the second toe of the opposite sympathectomized extremity (control) are shown as evidence of the absence of a circulating vasoconstrictor substance.

Pulsations were recorded from the second toe of each foot. In nine of these cases there was no constriction in the control extremity when the contralateral foot was cooled until no pulsations could be detected. In the other six cases, there were gradual decreases in the pulsations of the control toes varying from 30 per cent to 58 per cent. These changes might be attributed to a vasoconstrictor substance liberated by cooling the body, or to the local effect of the ambient temperature (68° F.) on the control foot. Since Elliot[6] and Ascroft[1] indicated that cold potentiates the action of epinephrine, the fact that these decreases did not occur when the control foot was kept warm would

not necessarily rule out a circulating vasoconstrictor substance. Therefore, five extremities (Nos. 8, 14, 15, 22 and 25) were cooled while the entire body except the head and feet was kept warm by an electric blanket. In all five cases the pulses actually decreased at slightly higher temperatures than when the same extremities were tested with the body exposed to cold (68° F.). This decrease in pulsations at slightly higher temperatures is probably due to the decrease in blood flow in the foot caused by the generalized vasodilatation produced by heating the body. A decrease in blood flow on warming the body frequently has been demonstrated in our laboratory in patients with sympathectomized extremities or in patients with extremities with decreased vasomotor activity due to obliterative arterial disease, and is in keeping with the "borrowing-lending phenomenon" as described by Ray, Burch, and DeBakey.[18]

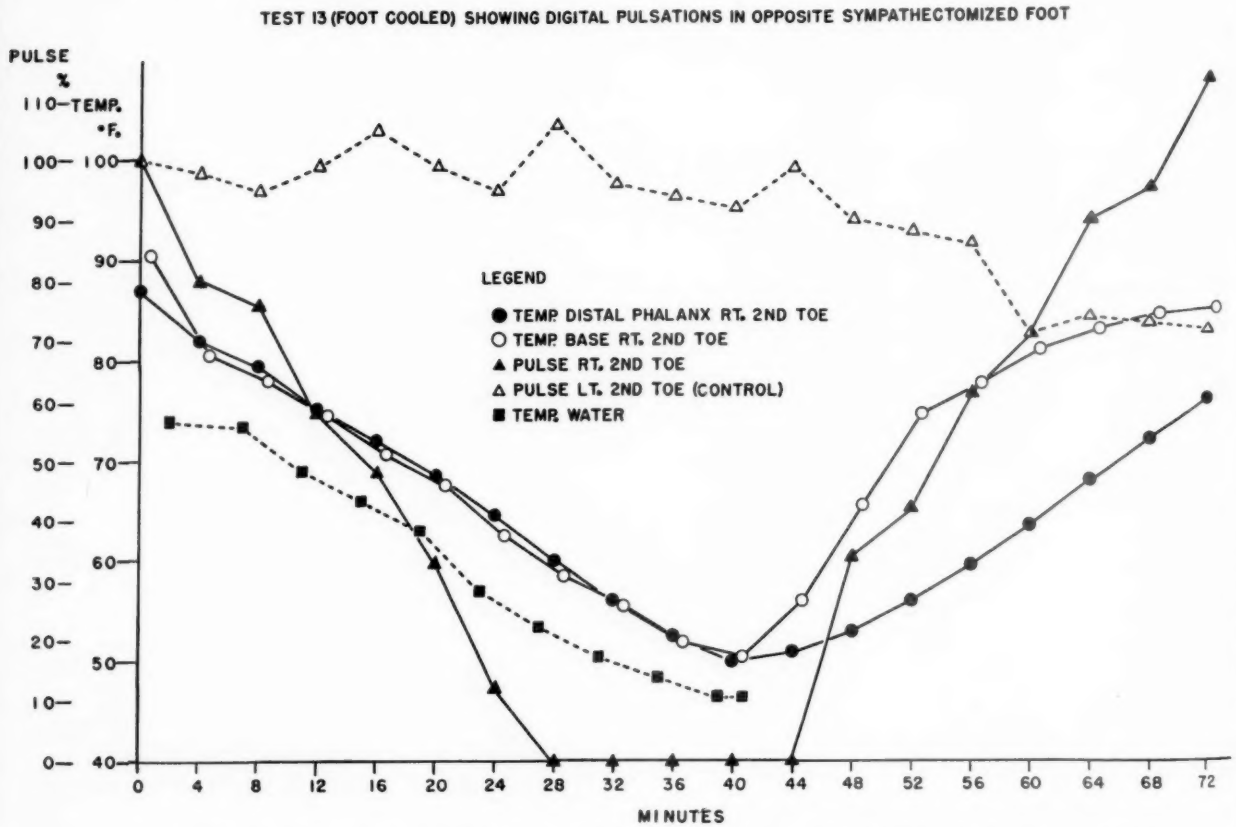

Fig. 5.—Illustrates another test and is similar to Fig. 4. In this study the amplitude of pulsations in the second toe of the opposite sympathectomized extremity (control) decreased 30 per cent during the period in the controlled temperature room (68° F.)

Five extremities were further studied by cooling only one toe while the remainder of the body was kept comfortably warm (room temperature 78 to 82° F.). Water was circulated through the plethysmograph cup and the temperature of the toe recorded every 30 seconds as described under Method. Plethysmographic tracings were made from the second and fourth toes, one acting as a control while the other was cooled. The graph (Fig. 6) is repre-

sentative of the results in all five tests and illustrates the marked decrease in pulsations produced in one toe with no appreciable effect on the control toe. This was evidence of the local nature of the reaction. The surface temperature reached before the pulsations became unrecordable was always lower using this method than when the whole foot was cooled. It was more difficult to cool the toe evenly by this method since the proximal portion tended to remain much warmer than when the whole foot was cooled. Precooling of blood, as described by Bazett and associates,[2] probably helped to account for the more even cooling by the first method.

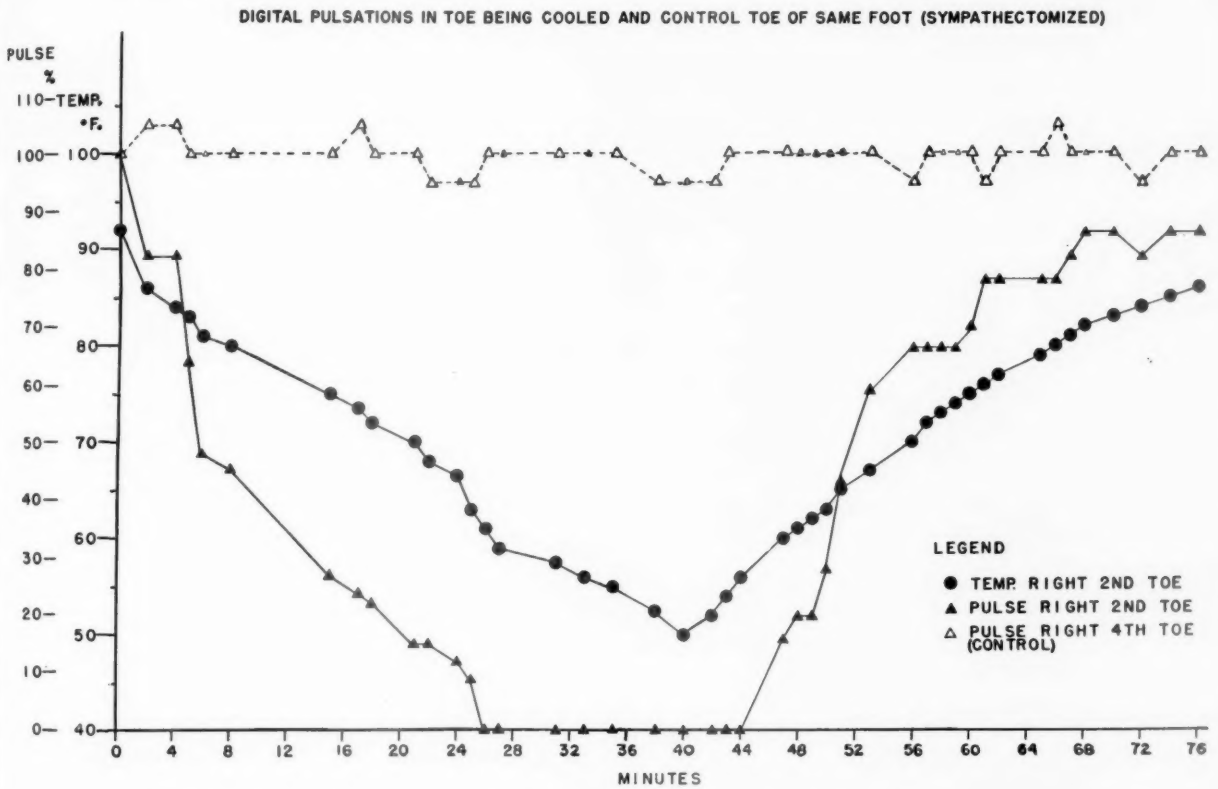

Fig. 6.—The graph demonstrates the local effect of cooling one toe of a sympathectomized extremity. The digital pulsations disappeared in the toe being cooled with no noticeable change in pulsations of another toe of the same foot.

While vasodilator metabolites undoubtedly are a factor in maintaining vasodilatation within certain limits of temperature, as postulated by Freeman, this factor was insufficient to explain our results. Five extremities (1, 2, 3, 4 and 9) developed definite cyanosis of the toes during the period of cooling. Several others showed questionable cyanosis. This was evidence that the blood supply was decreasing faster than the metabolic requirements. As would be expected, this occurred only in extremities which vasoconstricted at the higher temperatures. Another problem difficult to explain on the basis of metabolism alone was the rather sudden, uneven rate of vasoconstriction on cooling observed in many of the tests. This can be seen on the graph (Fig. 2)

summarizing the effect of cooling in twenty-five tests. In many of the tests marked decreases in pulsations took place with but a few degrees change in temperature. This was demonstrated even better on individual graphs of certain extremities showing pulse, temperature, and time relationship (Fig. 4). Perkins and associates[16] reported "sudden vasoconstriction" on cooling sympathectomized paws of cats and discussed its significance as evidence of the direct action of cold on the smooth muscle of the arteriole.

The possible role of sensory nerves in vasomotor activity needs further clarification. No change in reaction to cold could be noted in four of the sympathectomized extremities (Nos. 1, 2, 8, and 20) after anesthetization of the tibial nerve at the ankle. This block allows the possibility of overlapping from other sensory nerves. Further tests are planned with more complete anesthetization of the foot. Perkins and associates[16] found no change in the "critical temperature of sudden vasoconstriction" in the sympathectomized paws of cats even when the leg was disconnected from the body except for the procainized artery and vein. The importance of the "axon reflex" in maintaining vasodilatation in the sympathectomized extremity warrants further study.

SUMMARY

Considerable variation in reaction of the vessels to cold has been demonstrated in sympathectomized extremities with obliterative arterial disease. Extremities with more advanced obliterative disease usually vasoconstricted at higher temperatures than those with less disease. Too few cases of thromboangiitis obliterans were studied to permit comparison with the arteriosclerotic group, but in three out of five cases of the former studied, the extremities vasoconstricted at relatively high temperatures. Since certain cases showed marked vasoconstriction after prolonged exposure to air at temperatures varying from 65° F. to 70° F., this factor might become important clinically in the more advanced cases of obliterative arterial disease.

Various procedures have been used in an attempt to determine the factors responsible for vasoconstriction in these extremities. The rate of blood flow was important in determining whether or not an extremity would cool sufficiently at a given ambient temperature to cause constriction of the vessels. Under the conditions of our studies, circulating vasoconstrictor substances due to the action of cold on the body were of little significance. While vasodilator metabolites undoubtedly are a factor in maintaining vasodilatation, reasons are given for believing that a lack of these metabolites, due to the lowered metabolism of the part from cooling, was insufficient to account for our results. Our observations are in accord with those of Perkins and associates,[16] who showed that the vasoconstriction which occurred in the denervated and sympathectomized paws of cats on exposure to cold was a local reaction, probably due (1) to the action of cold on the smooth muscle of the arteriole and (2) to reduced formation of vasodilator metabolites from cooling of the tissues, as described by

Freeman. Further studies are being made in an attempt to determine the importance of local vasomotor reflexes of the "axon type" in vasoconstriction following sympathectomy.

The authors wish to thank Dr. E. M. Landis for his many helpful suggestions.

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A CRITIQUE OF LABORATORY METHODS IN PERIPHERAL VASCULAR DISEASE

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FOR several years we have been interested in the development of techniques that will permit an objective evaluation of the peripheral circulation. These techniques are not designed to establish diagnoses, but are intended to measure the degree of impairment of circulatory physiology. Ultimately, this should increase our knowledge of the physiology of the peripheral circulation and the pathologic processes that so commonly affect it. Our specific aims have been: (1) to obtain some objective estimate of the degree of impairment of limbs with arterial insufficiency, (2) to develop a battery of tests which will help us to select patients who will or will not have significant improvement in their peripheral circulation following sympathetic ganglionectomy, and (3) to obtain an objective measure of improvement, or lack of it, after various types of conservative and surgical therapy.

At this time, there is no practical method of measuring the blood flow to a human extremity directly, so indirect methods must be used. The effects of arterial insufficiency on muscle function, skin temperature responses, and digital and limb pulsations are studied.

Muscle function is evaluated by walking and ergometric test. Both are sufficiently discriminative to be of value. Limb pulsations are measured by a standard oscillometer. This is not very informative because calibration of the instrument is impossible and its sensitivity low. It may be possible to correct these defects and increase the significance of oscillometric studies.

Skin temperature responses to changes in environmental temperature and to anesthetization of the appropriate peripheral nerve with procaine are distinctly informative as long as certain inherent limitations are appreciated. Digital pulsations, as measured by a plethysmograph, correlate well with skin temperature responses, have the advantages of a wider range and a quicker response, and are not affected by sudomotor activity. In addition, there are certain physical characteristics of the plethysmogram that open new fields of study.

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Tests of sudomotor activity are of value for checking the completeness of sympathetic denervation, especially in areas where the plethysmograph cannot be used and skin temperature changes are of small magnitude.

WALKING TEST

Intermittent claudication is the most common symptom complex encountered in patients with occlusive vascular disease. It is quite natural, then, that the patient and his physician judge therapeutic effectiveness by improvement in the patient's ability to walk without pain. However, serious errors in interpretation may be made if this change in walking ability is not measured objectively. In estimating the ability of a patient to walk, it is essential to characterize the result not only by the distance walked but by the rate of walking (Barker, Brown, and Roth[1]). In this laboratory, the rate of walking is fixed by means of a metronome. The patient walks over a measured, level course accompanied by a technician who maintains cadence and encourages the patient to walk as far as possible. If the patient walks a full mile, he is stopped and considered to be within the limits of normal for this test. In isolated instances, only, has it been necessary for a patient to stop in the middle of the course which is 60 feet long. The distance walked by the same patient at different times is reasonably constant.

TABLE I. THE EFFECT OF THE RATE OF WALKING ON THE TOTAL DISTANCE (IN FEET) WALKED BY SEVENTEEN CONSECUTIVE PATIENTS WITH INTERMITTENT CLAUDICATION

PATIENT	120 STEPS PER MINUTE	100 STEPS PER MINUTE	IMPROVEMENT (PER CENT)
H. A.	1,080	1,200	11
H. D.	2,960	5,280	78+
H. D.	720	960	33
H. S.	1,680	5,280	214+
A. G.	1,320	2,040	55
B. S.	420	480	14
H. L.	1,440	5,280	267
J. B.	1,560	5,280	238+
I. W.	960	5,280	450+
A. Y.	3,360	5,280	57+
E. W.	660	1,080	64
R. T.	840	1,200	43
C. F.	840	2,760	229
F. H.	1,080	1,320	22
M. F.	1,200	1,200	--
J. L.	840	1,560	86
M. H.	600	1,320	120

One reason subjective improvement of intermittent claudication is easier to obtain than is objective improvement is that the patient learns to walk at a slower gait. Table I shows the results of the walking test for seventeen consecutive patients with intermittent claudication. The performance of these patients when walking at the rate of 120 steps per minute was compared with the performance when walking at the slower rate of 100 steps per minute. A

rest period of at least thirty minutes was allowed between tests. Alternate patients walked at the faster rate first and the slower rate second. Thirteen of seventeen patients (77 per cent) walked a distance at least 33 per cent greater at the slower rate of 100 steps per minute than at the faster rate of 120 steps. It is impossible to calculate the average per cent of improvement because six patients walked the full mile and were stopped. However, it is in excess of 116 per cent.

ERGOMETRY

The development in a limb of a fatigue or of pain with exercise is conditioned by the functional efficiency of the arterial circulation. Various methods have been used to measure the amount of work done by muscles before fatigue or pain limits the exercise.

In this laboratory, an ergometer has been used which tests the ability of the muscles of the extremity to contract against progressively increasing resistance.[14] As with other ergometers, it is difficult to control the effect of the will on the performance, and it is difficult to be absolutely certain that muscle groups other than those under investigation are not contributing to the total effort. It is possible, however, to test a limb with deficient circulation against the normal limb in the same subject, and when standards are set up for control groups of the same sex and age, it is possible to make gross estimates of the part played by the will and of the capacity of the muscles of the individual extremity to perform work.

TABLE II. ERGOMETRIC PERFORMANCE, LOWER EXTREMITIES (IN MM. HG)*

	RIGHT	LEFT
46 Normal Adult Males		
Mean	720	664
Standard deviation	156	158
Standard error of mean	26.3	26.6
29 Male Patients With Intermittent Claudication		
Mean	206	213
Standard deviation	145	90
Standard error of mean	27	17

*A small number of adult males over the age of fifty with no symptoms or signs of arterial insufficiency of the lower extremities have been studied, and their ergometric performance falls within the normal variation for adult males.

The test is performed with the patient sitting in a chair, the position of which is adjustable, on a wooden platform. The seat is low so that the thigh is flexed at the hip in such a manner that depression of a pedal with the foot is accomplished almost entirely through contraction of the plantar flexors in the calf. Beneath the pedal is a 60 c.c. rubber bulb which is compressed and emptied by the pedal, whereby expressing the air from the bulb into a five-gallon carboy. The pressure within the carboy increases until it is high enough to compel the subject to abandon the test. The rate of exercise is regulated at 40 compressions per minute by means of a metronome. When the bulb is emptied completely a light flashes to notify the patient. For the upper extremity, the bulb is com-

pressed in the hand, thereby testing the muscles of the forearm. The subject is urged to continue the exercise until the limit of his endurance is reached and he reports the development of uncomfortable sensations and of fatigue.

To be sure, this apparatus leaves much to be desired. Nevertheless, it has proved useful in the study of arterial insufficiency. The performance is significantly lower in patients with obliterative arteriosclerosis than in normal adult men. Sufficient data are not available, at this time, to evaluate the effect of age alone on the ergometric performance in the presence of a normal arterial circulation (Table II).

OSCILLOMETRY

Oscillometry is a mechanical method of measuring the pulsations of the soft parts of a limb. It depends on the resilience of the tissues and the patency of the large arteries to provide a pulsating head of pressure. The collateral circulation has a very weak pulsatile force. Oscillometry, as currently performed, is little more informative than is palpation of the pulses, but it is more sensitive than our finger tips and gives an objective record for purposes of comparison and future reference. Saint[7] has called it a measure of the "Penultimate" arterial pulse deflection as contrasted with digital plethysmography which is a measure of the arteriolar, or "Ultimate" arterial pulse.

The development of oscillometry has been hindered by the difficulty in quantitating the pulse deflection or oscillation. If we wish to know the volume of the pulse deflection, it is necessary to measure, or standardize, the volume of the part, and to use a low-pressure measuring device as is done in digital plethysmography. To measure the size of the arms, forearms, thighs, calves, and ankles of each patient would require time and effort incommensurate with the information obtained from the test. And, in order to employ a low-pressure system, we would need a rigid cup that is fitted to the limb with an air-tight seal. This, too, is impractical. Accordingly, oscillometric studies are made with a flexible cuff that can be applied quickly to limbs of various sizes. But, to obtain a recordable pulse with such a cuff, pressure must be applied to make the coupling between the cuff and the extremity tight enough to transfer energy maximally, and therefore we are dealing with a relatively high-pressure system. Under these conditions, volummetric calibrations are not satisfactory, and the production of an instrument that will record these oscillations in terms of pressure is a worth-while step.

When a high-pressure transducer is attached to the Grass Electroplethysmograph it becomes a recording oscillometer and affords an opportunity to study the character of the pulse wave as well as the amplitude of the individual pulse deflection. Fig. 1 shows a tracing of oscillations of a normal calf and one with advanced obliterative arterial disease. In the latter tracing the amplitude of the machine has been increased five times, so we can say that the pressure developed is one fifth that of the normal limb. When this tracing was made we were unable to calibrate in terms of millimeters of mercury. The difference in the character of the waves is striking.

SWEATING TESTS

It is often desirable, for the evaluation of neurovascular problems, to have a measure of the degree of sweating. Denervation abolishes reflex sweating in most areas of the skin and such information has been useful for evaluating the completeness of sympathetic denervation. It is recognized, too, that activity of the sweat glands varies in different types of vascular diseases and with different severities of the disease, as in arteriosclerosis obliterans. The possibilities in this regard have not been explored fully, however, because a satisfactory and convenient method for quantitating the production of sweat has not been available.

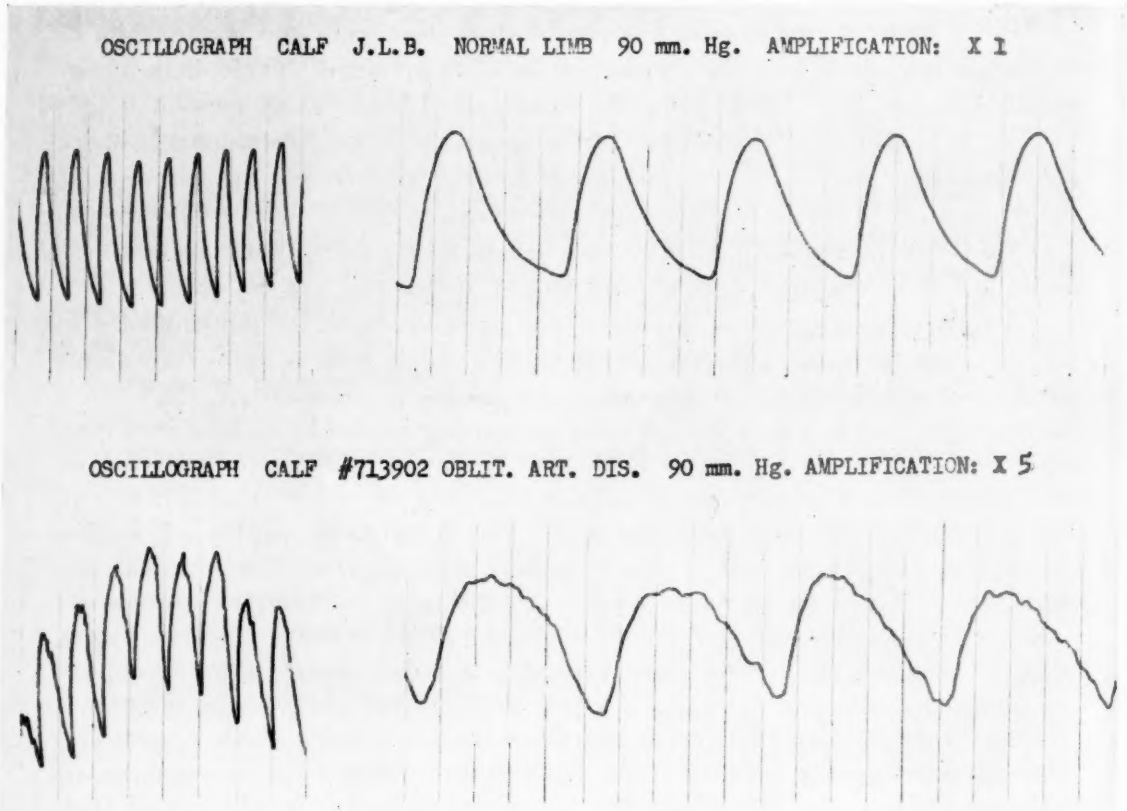
OSCILLOGRAPH CALF J.L.B. NORMAL LIMB 90 mm. Hg. AMPLIFICATION: X 1
OSCILLOGRAPH CALF #713902 OBLIT. ART. DIS. 90 mm. Hg. AMPLIFICATION: X 5

Fig. 1.—Oscillograph of a normal calf (above) and calf of a limb with advanced occlusive vascular disease (below). Amplification is five times greater in lower tracing.

Techniques for exciting the sweat glands reflexly still lack standardization. The use of a heat cradle over the trunk and thorax, affording ambient temperatures as high as 140° F., has not proved satisfactory in all cases. Electrically heated blankets covered by rubber sheets and woolen blankets have been more satisfactory, and it is believed that the optimum stimulus for inducing sweating is to expose the subject to an environmental temperature at or just above body temperature with a relative humidity of about 90 per cent.

Chemical agents for stimulating the sweat glands, such as pilocarpine, have not been advocated because they act directly on the effectors, for the most part, and are useless for studying reflex sweating. The unpleasant general reactions they induce in patients make them unpopular.

Techniques for detecting the presence or absence of sweating are simple. The use of chemicals which change color with hydration has been very popular. They are most useful when photography is employed for recording the areas of skin which are sweating. They have the practical disadvantage, however, of staining bed bed linen and clothing. A further disadvantage lies in the fact that it is difficult to estimate, even roughly, the degree of sweating by these methods.

The fact that epidermis is an electric insulator when dry, and becomes a good conductor when wet with perspiration is utilized in the electrical method for detecting the presence or absence of sweating. By measuring the resistance the skin offers to passage of a minute electric current (Richter and Woodruff[13]) it is possible to make some estimate of the activity of the sweat glands in the area of skin under investigation. Objections to this technique lie in the possibility that readings may be complicated by polarization since direct current is used, and in the fact that the resistance will vary according to the size of contact between the electrode and skin surface. In other words, the size of the electrodal junction is as important as the properties of the skin iteslf, if not more so.

Attempts have been made to devise an apparatus that utilizes alternating current and with which the area of contact can be used as a measurable variable. Technical difficulties have been encountered, however, and the neurodermometer devised and modified by Richter and Woodruff[13] is still the most practical instrument available for detecting the presence or absence of sweating and for estimating, roughly, the degree of sweating. By this method, for instance, it can be demonstrated that removal of the twelfth thoracic to fourth lumbar sympathetic ganglia, inclusive, paralyzes sudomotor activity completely below the tibial tubercle.

SKIN TEMPERATURES

An eight-lead, automatically-recording potentiometer* is used in this laboratory to measure skin temperatures. Each lead consists of a filament of iron and constantan soldered together at the distal end to form a thermocouple. The current flowing between the two metals is proportional to the temperature at their junction. The machine amplifies the minute currents and records them on a moving paper which bears a temperature scale. The leads record in succession at thirty-second intervals. A continuous record is thus obtained and changes within one-fourth of one degree Fahrenheit can be read.

The temperature at the skin surface is a resultant of many factors, as indicated by Table III. These factors may be likened to buffers that tend to im-

*Brown Instrument Co., Division of Minneapolis-Honeywell Regulator Co., Philadelphia, Pa.

pede sudden changes. The effect of some of these factors on the skin temperature at any one moment can be diminished, or eliminated, by various means, such as: by studying changes within the individual rather than absolute values, by having the subject at rest, in a constant position, and in the fasting state, by conducting the study in a room with controlled temperature, humidity, and air movement, and by allowing sufficient time for equilibration. Under these circumstances, changes in skin temperature will reflect (quite accurately) the direction of change of blood flow. On the other hand, it is possible for sudden changes in blood flow to occur without corresponding changes in skin temperature. This is especially true when the subject is vasodilated. Furthermore, since the temperature of the skin is approaching its physiologic limit when the subject is vasodilated, we would expect that relatively large increases in blood flow would be necessary to bring about a slight increase in skin temperature. Consideration of these factors may explain the poor correlation between skin temperatures and blood flow observed by Fetcher, Hall, and Shaub.[5]

TABLE III. FACTORS INFLUENCING THE SKIN TEMPERATURE OF A DIGIT

- A. The temperature of the blood
- B. The velocity and quantity of blood flow
  - 1. Cardiac output
  - 2. Patency of the blood vessels
  - 3. Responsiveness of vessels to sympathetic stimulation
  - 4. Intact sympathetic nerve pathways
  - 5. Activity of vasomotor center
  - 6. Basal metabolic rate
  - 7. Position of the digit in relation to the heart
  - 8. Type and quantity of ingested food and elapse of time
- C. Thickness and quality of skin and subcutaneous tissue
- D. Sudomotor activity
  - 1. Number of sweat glands in part
  - 2. Ability of glands to respond to stimulation
  - 3. Intact sympathetic nerve pathways
  - 4. Activity of the sympathetic system
    - a. Acute and chronic emotional states
- E. External environment
  - 1. Air temperature and movement
  - 2. Radiation
  - 3. Humidity
  - 4. Completeness of exposure
  - 5. Duration of exposure

Another pitfall in the proper interpretation of skin temperatures is the fact that only a small part of the normal maximal blood flow is needed to warm the skin to levels considered to be evidence of significant vasodilatation.[7] Table IV lists eight extremities in which the temperature of the great toe reached 90° F. or higher after tibial nerve block in a room at 68° F., in spite of the fact that the pulse deflection of the second toe is significantly below the normal mean of 4 c.mm. per 5 c.c. of part, as established by Burch, Cohn, and Neumann.[3]

Many methods of ablating sympathetic vasoconstrictor tone have been advocated. Direct heating invalidates skin temperature studies but may be used for plethysmographic studies. Reflex heating, as described by Lewis and Pickering,[10] by means of a heat cradle placed over the abdomen and thorax, has, in our hands, failed to give consistent results even in normal subjects.

TABLE IV. MAXIMUM RISE IN SKIN TEMPERATURE OF GREAT TOE VS. MAXIMUM PULSE DEFLECTION OF SECOND TOE AFTER TIBIAL NERVE BLOCK IN EXTREMITIES WITH OCCLUSIVE VASCULAR DISEASE

PATIENT	NUMBER	TOE	TEMPERATURE* (IN ° F.)	PULSE (IN C.MM./5 C.C. OF PART)
J. B.	736130	R	91.5	0.8
F. P.	242107	R	92.0	2.5
		L	90.0	2.8
H. F.	135388	R	90.5	0.7
V. H.	725191	L	90.0	1.9
D. G.	679220	L	90.0	1.7
F. M.	701129	L	91.5	0.4
H. R.	700487	R	91.0	2.2

*Room temperature: 68 to 70° F.

Landis and Gibbon[9] found that all normal subjects have significant reflex vasodilatation (i.e., warming of the digital temperature to 89.6° F. or more) within 30 minutes, when the other two extremities are immersed in water at 113° F. They concluded that vasodilatation within this period rules out significant organic occlusion and that the inability to dilate to this level within this time is due to organic changes within the arterial walls. They also pointed out, however, that it is not always possible to release vasospasm by this method either in vasospastic or occlusive arterial disease, and the vasospasm could be released by blocking the appropriate nerve with procaine. This is just the point that limits the usefulness of the test.

Unless a test is used that will make it possible to rule out the element of vasospasm, it will not be critical enough to select patients for surgery. We have observed patients with obliterative arterial disease who show no evidence of reflex vasodilatation by this method in 30 minutes and yet are maximally dilated in one hour, ninety minutes, or two hours. Some patients have no rise in skin temperature after two hours of immersion but have a significant temperature rise after a peripheral nerve block.

Another limitation of reflex vasodilatation, or of any method of generalized vasodilatation, as a criterion for selecting patients for surgery, is the fact that the limb with advanced occlusive disease may cool, and its pulses diminish, when the vessels of the rest of the body are dilated. Thus same limb may then have an increase in temperature and digital pulsations when the vessels of the rest of the body are vasoconstricted, or after nerve block or sympathectomy. This phenomenon has been termed "Hemometakinesia" by

Ray, Burch, and DeBakey.[12] We believe it is due to the inability of the patient's cardiovascular system to maintain the blood pressure in the extremity in the presence of generalized vasodilatation.

In our hands, blocking of the tibial nerve at the internal malleolus is the most reliable method for releasing sympathetic vasoconstrictor tone. However, it is not always effective, and a possible explanation for occasional failure is discussed elsewhere in the JOURNAL.[2]

DIGITAL PLETHYSMOGRAPHY AND BLOOD FLOW

Digital plethysmography affords a convenient method for measuring the pulsatile blood flow to a digit. It makes possible the quantitative measurement of the increase in size of the digit produced by a momentary excess of inflowing over outflowing blood. It also allows the study of the character of

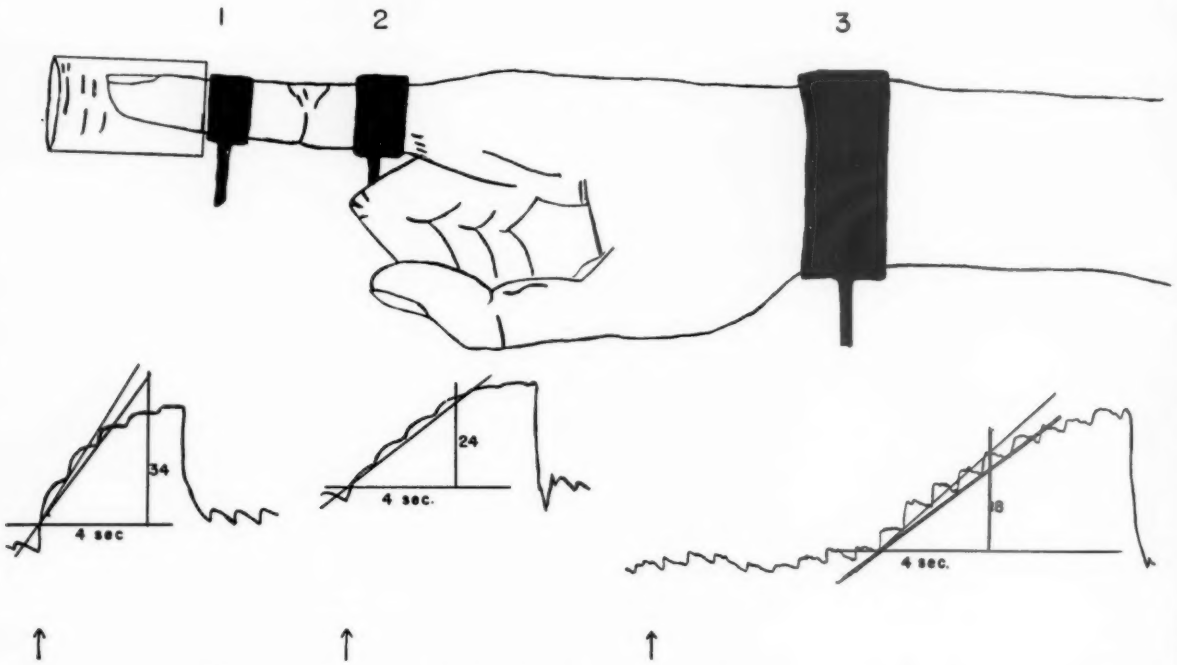

Fig. 2.—Diagram showing a collecting cup on the distal phalanx and three positions of the occluding cuff. Below are representative tracings in each case. The difficulty in drawing a straight line between successive pulse deflections is evident. Note the artefact with the cuff in positions 1 and 2, and the lag period in position 3.

the pulse deflection and pulse waves in health and disease. Of great practical significance is the fact that the variations in pulse amplitude between normal digits and those with arterial insufficiency, and between the same digit in the state of vasoconstriction and in the state of vasodilatation, are of sufficient magnitude to be measured easily. In other words, it is possible to measure, with considerable accuracy, changes occurring in a part of the body in which peripheral occlusive vascular disease plays the greatest havoc. Gangrene of the digit more commonly leads to catastrophe than does intermittent claudication.

Burton[4] observed a close correlation between the volume of the pulse and the rate of blood flow in the digit as determined by the method of Hewlett and Van Zwaluwenburg.[8] There is likewise a close correlation between the volume of the pulse and the skin temperature within limits. It is obvious that an expanded pulse volume with a drop in blood pressure may actually be associated with a decreased rate of blood flow. The large pulse oscillation in aortic regurgitation does not necessarily represent a large rate of blood flow.

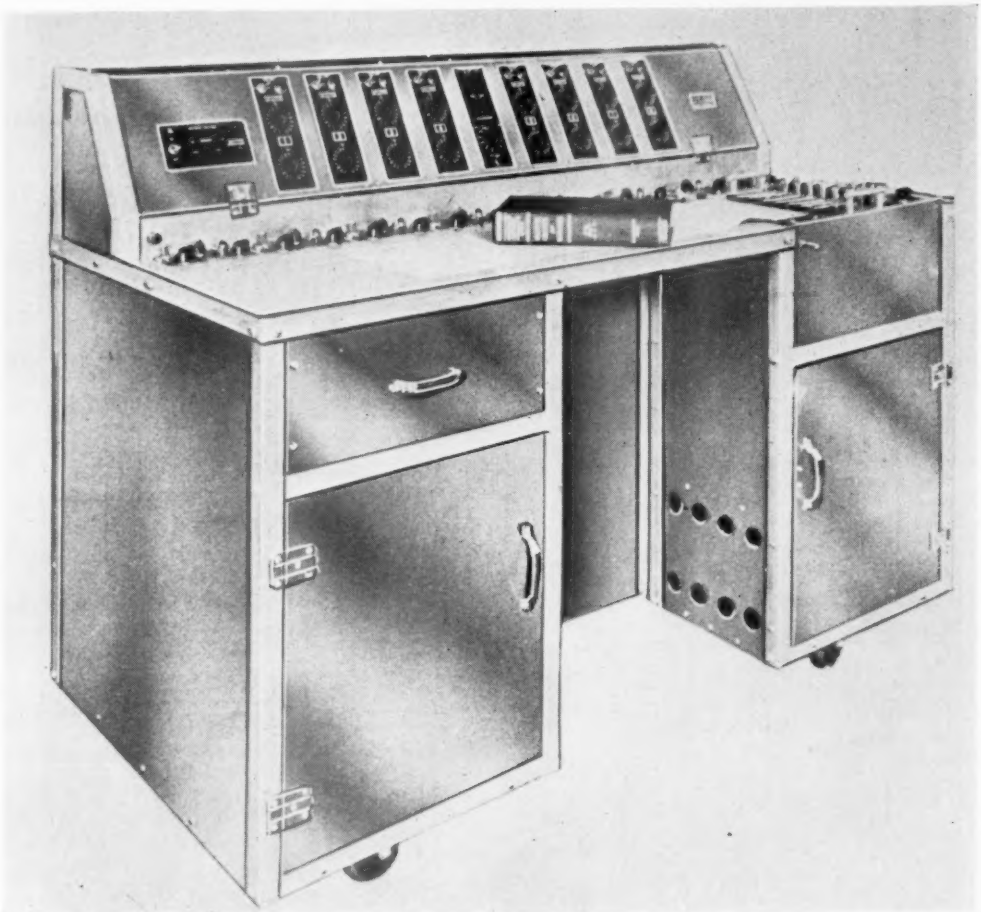

Fig. 3.—The Grass Electroencephalograph.

A digital plethysmograph may be used to measure blood flow by the venous occlusion method of Hewlett and Van Zwaluwenburg,[8] but certain intrinsic difficulties make it less practical than the study of digital pulsations. In Fig. 2 is seen a collecting cup on the distal phalanx of a finger, and three positions at which an occluding cuff may be placed. Position 1 is considered to be ideal because practically all of the part being filled is included in the collecting cup. However, because of the small size of the part, filling occurs rapidly and the slope may reach a plateau within two or three pulsations. When this occurs it is difficult, and sometimes impossible, to draw a straight

line through corresponding points of the digital pulse. In addition, a large artefact is usually seen with the cuff in this position. If the occluding cuff is placed in position 2, it is easier to measure the slope, but the objection is that the tissues between the cuff and the cup must fill before the distal phalanx begins to fill. In this position, also, an artefact is frequently observed.

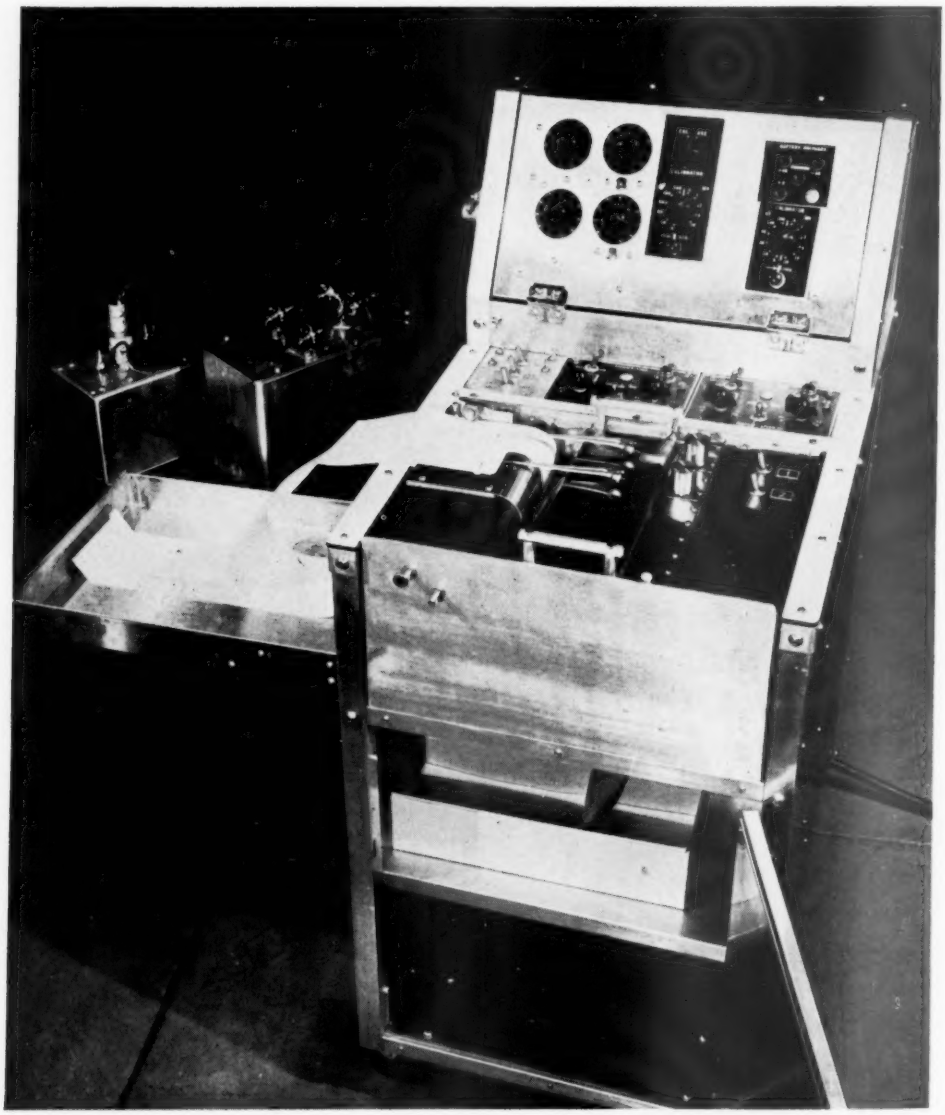

Fig. 4.—An experimental, two-channel electroplethysmograph.

Wilkins, Doupe, and Newman[15] concluded that error resulted if the occluding cuff were placed at a distance from the collecting cuff, especially if it were placed at the wrist. Goetz[7] pointed out that the results obtained with the cuff on the finger were exactly three times those obtained when it was on the wrist.

On theoretical grounds, placing the cuff on the wrist is objectionable because part of the filling of the distal phalanx could be retrograde from the veins of the hand. In fact, rapid distention of the phalanx could occur in the presence of complete occlusion of the digital arteries. In practice, we find that although linear slopes may be obtained at high rates of flow, at lower rates it may be just as difficult to draw a straight line through the pulse deflections as it is when the cuff is in position 1. We have seen an occasional example, in a vasoconstricted digit, of a steeper slope with the cuff on the wrist than with the cuff on the finger adjacent to the cup. This might be explained on the basis of retrograde filling in the presence of constricted

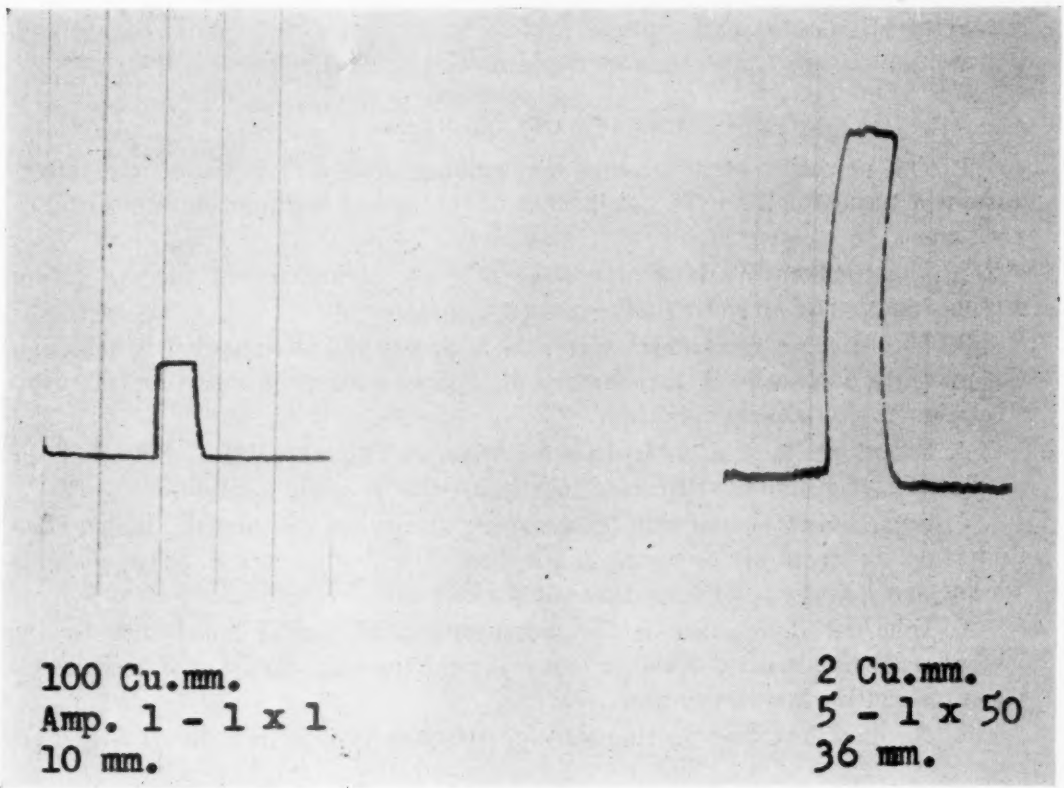

Fig. 5.—Grass Electroplethysmograph. Grass transducer over-all sensitivity.

arterioles of the finger tip. The lag period between venous occlusion and the measurable increase in volume of the digit varies considerably in the same patient at different times. We have been unable to demonstrate a constant relationship between the values for the rate of blood flow obtained by venous occlusion at the wrist and venous occlusion at the finger adjacent to the plethysmograph cup.

During the past three years the Grass Electroencephalograph* has been adapted for use as a plethysmograph. The unmodified machine consists of eight independent amplifiers and eight direct-writing recorders. It amplifies

*Grass Instrument Company, Quincy, Mass.

and records action potentials and is useful as an electroencephalograph, electromyograph and electrocardiograph (Fig. 3). Addition of a demodulating unit to this apparatus enables it to amplify the output voltage of a transducer which converts mechanical energy to electrical energy by means of a strain gauge. Thus, pressure variables such as digital and limb pulsations, and arterial and venous pressures can be measured. Fig. 4 shows a two-channel model.

Fig. 5 indicates the over-all range and sensitivity of the machine with a low pressure transducer.* On the left can be seen the deflection caused by an injection of 100 c.mm of air at the lowest amplification, and on the right, the deflection caused by an injection of 2 c.mm. at the "noise" level. This latter injection was made into a system containing 3,200 c.mm. of air and represents, therefore, a volume increase of one part in 1,600.

SUMMARY AND CONCLUSIONS

1. The necessity of measuring the walking ability of patients with intermittent claudication and the significance of the rate of walking on total distance are stressed.

2. The Simeone-Watkins ergometer is a useful instrument for evaluating muscle function of an individual extremity.

3. The Richter neurodermometer is a practical instrument for detecting the presence of sweat. A satisfactory method of measuring sweating quantitatively is not available at this time.

4. Some mechanical difficulties of quantitating the pulse deflection, or oscillations, of a limb are discussed together with a possible solution.

5. Some limitations of skin temperature studies are mentioned. Reflex vasodilatation by warm air or water is not discriminative enough to select patients for surgery because it does not rule out the element of vasospasm.

6. Inherent difficulties in the measurement of digital blood flow by the venous occlusion method make it less practical than the study of digital pulsations for routine laboratory use.

7. A versatile, direct-writing electroplethysmograph is introduced.

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DIRECT AND RETROGRADE AORTOGRAPHY

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WHILE the technique of aortography is not new, its growing importance in the field of vascular surgery has been apparent only in the past few years. Certain vascular surgeons in America such as Blakemore,[1] and a few others who were concerned with the treatment of aneurysms of the great vessels, recognized the practical value of visualization and made use of it during operation on occasion. However, it was little more than a decade ago that direct aortography was introduced into this country by the urologist. The rapid expansion of vascular surgery, especially in the realm of congenital heart disease, during the past decade, and the advent of angiocardiography with its occasional failure to demonstrate the thoracic aorta satisfactorily have encouraged further development of aortography.

The techniques for visualizing blood vessels date back to 1923, when the use of iodized oil and strontium bromide for roentgenologic demonstration of peripheral arteries was reported.[2, 3] These materials proved unsatisfactory and dangerous. In 1924, Brooks[4] introduced aqueous sodium iodide as a relatively safe agent. Although dos Santos considered concentrations of over 30 per cent too irritating for peripheral arteriography, he did employ concentrations of up to 100 per cent with safety in his technique of translumbar aortography.[5-8]

Thorotrast, also used for hepatosplenography, gained an early but transient wide popularity in angiography because of its excellent radiopacity and the usual absence of immediate reactions. In the early thirties, certain organic iodide compounds employed for intravenous urography came into increasing use in angiography. Although compounds such as Hippuran, Skiodan, and Tenebryl have been employed, the most popular among these contrast media in America have been iodopyracet (Diodrast) and iodoxyl (Neo-Iopax). Another contrast medium, Urokon, is being investigated currently. Although satisfactory angiography has been possible with all of these compounds, we were interested in studying a few used most commonly in aortography.

EVALUATION OF CONTRAST MEDIA

A. Physical Characteristics

1. Thorotrast†[7] is supplied commercially as a 25 per cent colloidal suspension of thorium dioxide (ThO_2). Thorium is a heavy radioactive metal of the tin group and is only moderately radiopaque in vitro (Fig. 1). The suspension is a light brown translucent liquid.

2. Sodium iodide (NaI) has been used most often in a concentration of 80 per cent. The salt contains 85 per cent iodine and is very radiopaque (Fig. 1).

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†Heyden Chemical Corporation, New York, N. Y.

When ready for use, the solution is a colorless liquid. On deterioration, especially after exposure to air or light, the liquid soon becomes deep yellow. Occasionally, autoclaving turns the solution a pale yellow color without making it unsuitable for use.

3. Iodopyracet[10] or Diodrast* is the diethanolamine salt of 3,5-diiodo-4-pyridone-N-acetic acid. The salt contains 62 per cent iodine and is moderately radiopaque (Fig. 1). It is supplied commercially in concentrations of 35 and 70 per cent. The colorless solution has a neutral reaction. On exposure to air or cold, the salt readily crystallizes out of solution.

Fig. 1.—Relative radiopacity in vitro of contrast media used in aortography. Calibrated Pyrex tubes contain distilled water as a control (*C*), 75 per cent iodoxyl or Neo-Iopax (*N*), 70 per cent iodopyracet or Diodrast (*D*), 80 per cent sodium iodide (*I*), and 25 per cent Thorotrast (*T*). The sodium iodide is the most radiopaque, with Thorotrast being the least dense.

4. Iodoxyl[10] or Neo-Iopax† is the disodium salt of N-methyl-3,5-diiodo-4-pyridone-2:6-dicarboxylic acid. The salt contains 51 per cent iodine and is moderately radiopaque (Fig. 1). It is supplied in concentrations of 35 and 75 per cent. The colorless solution has a neutral reaction. The salt does not readily crystallize out of solution on exposure to air.

B. Cardiovascular Effects

In a series of dogs and human patients, the arterial pressures in the brachial or carotid, and femoral arteries were measured directly through fine indwelling vinyl plastic catheters connected to Lilly capacitance manometers. A simultaneous electrocardiogram was obtained, and, in some instances, superior vena caval pressures via the right jugular vein were also obtained.

In 6 dogs, these contrast media were injected rapidly through a polyethylene catheter into the thoracic aorta via the left common carotid artery. The dosage

*Winthrop-Stearns, Inc., New York, N. Y.
†Supplied by Schering Corporation, Bloomfield, N. J.

ranged from 2 c.c. to 8 c.c. and the order of the agents was varied, so as to avoid effects due possibly to adaptation or accumulation. Seven human patients were studied. Both 75 per cent iodoxyl (Neo-Iopax) and 80 per cent sodium iodide were used via the translumbar route in two patients anesthetized by Pentothal Sodium. In three others, only iodoxyl (Neo-Iopax) was injected into the abdominal aorta, with only local anesthesia employed. In a similar patient, 25 per cent Thorotrast was used. One patient had 50 per cent iodopyracet (Diodrast) injected into the thoracic aorta via the left common carotid artery.

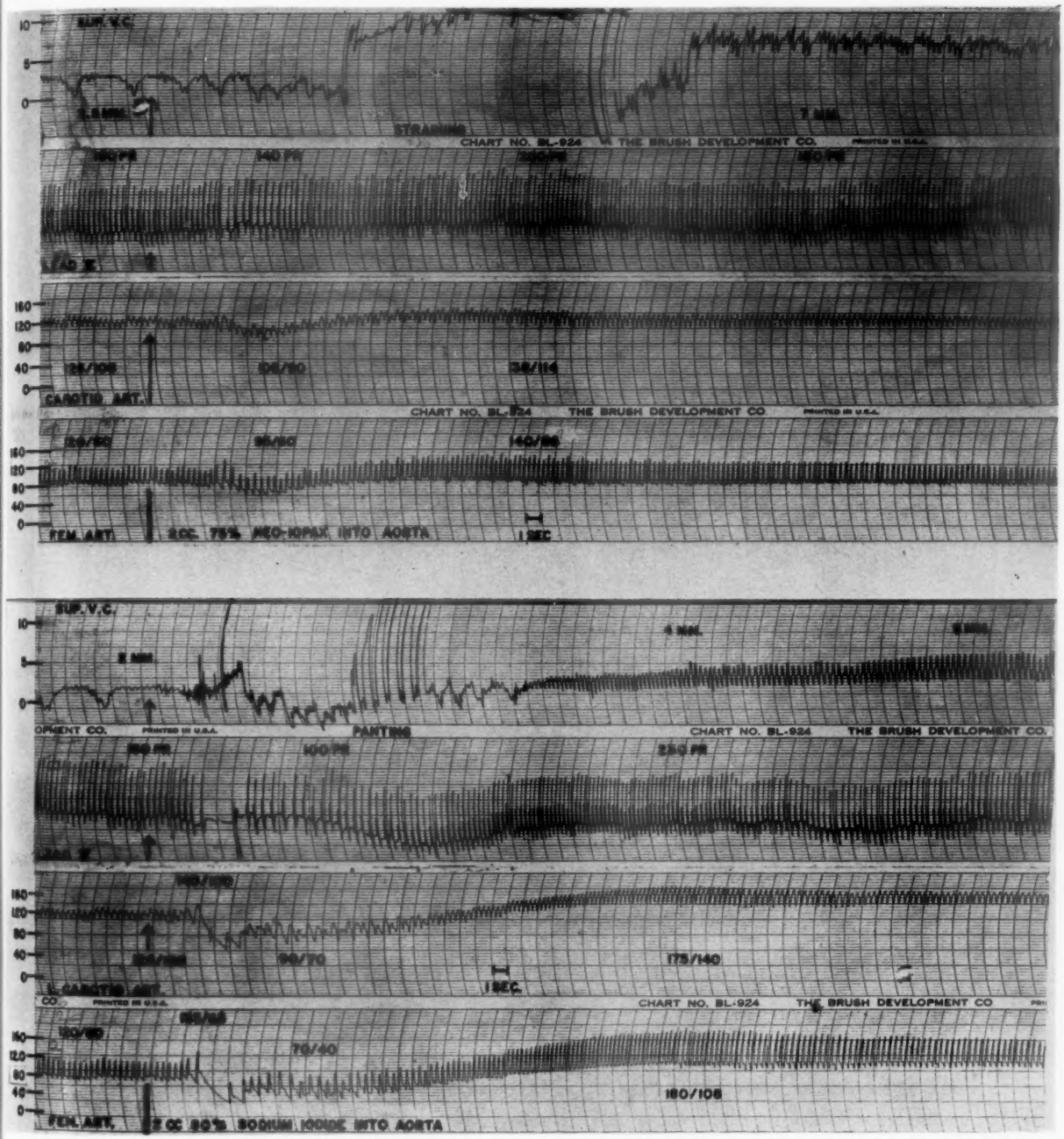
An analysis of over 25 injections in dogs and of 9 injections in human beings revealed a consistent pattern of cardiovascular alterations, regardless of the contrast medium tested. Coincident with the rapid injection of a small volume of the contrast medium, there was a slight elevation of the systolic and diastolic pressures in the carotid or brachial artery lasting only one pulse wave. The femoral arterial tracings also showed a slight elevation of the diastolic pressure, with or without rise in systolic pressure (Fig. 2, *A* and *B*). Injection of comparable amounts of 0.85 per cent saline solution likewise produced these effects, apparently as a mechanical phenomenon. With the larger volumes used in the human patients, the effect was greater and more prolonged in the upper trunk, and in one case, the femoral pulse was actually damped out during the injection (Fig. 3).

Three to six seconds following the injection of any of the contrast media, a hypertensive beat or two would initiate a period of hypotension lasting from a few seconds to over a minute. A distinct bradycardia was noted during the hypotension, but was usually of shorter duration. Seen only in dogs, an asystole often occurred at the onset of this period (Fig. 2, *B*), most consistently with sodium iodide, or the other iodides in injection doses of over 4 c.c. Associated with the bradycardia, there were occasionally noted a few ventricular extrasystoles, usually after the larger doses. Next there occurred a much longer period characterized by hypertension, mostly systolic, with great increase in pulse pressure. This was always associated with a tachycardia, and lasted usually from one-half minute to five minutes. In some human patients, the hypertension persisted for a much longer period. The increased pulse rate usually subsided before the alterations in blood pressure, as was observed in the case of the bradycardia and hypotension (Fig. 2, *A* and *B*). In 2 dogs, the measurement of the caval pressures revealed an increase most marked during the period of hypertension and tachycardia (Fig. 2, *A* and *B*).

These alterations were scarcely noticeable with Thorotrast. With Diodrast, the changes were greater, but still of a minimal degree. After some injections, only the transient hypotensive phase with bradycardia was observed. This same pattern has been reported occurring to a greater degree in dogs after intravenous injection.[11] Iodoxyl (Neo-Iopax) appeared to cause moderate vasomotor changes rather consistently. Most marked without question, and often severe in dogs, was the degree of these alterations when sodium iodide was injected.

The very short interval between the injection and the beginning of cardiovascular changes suggests that the vasomotor reactions observed after injection

A.



B.

Fig. 2.—*A*, Record of the cardiovascular effects of injecting iodoxyl (Neo-Iopax) into the aorta of a dog. There is a bradycardia and hypotension beginning four seconds after injection, followed by a tachycardia and hypertension. During the latter phase, the superior vena caval pressure rises and there is an increase in pulse pressure of the arterial tracings.

B, Record of the cardiovascular effects of injecting sodium iodide into the aorta of a dog. The bradycardia and hypotension begin two seconds after injection and are rather marked, initiated by an asystole of two seconds. The subsequent hypertension and tachycardia are associated with a wide pulse pressure. The superior vena caval pressure rises during this period.

of these contrast media into the aorta may be initiated in the splanchnic area and the arteriolar beds of the lower extremities. The pattern of response in the dog was not altered by section of both vagus nerves in the neck, and this has been noted by others, when iodopyracet was injected intravenously.[11]

Toxicity

1. Thorotrast: Although there is generally no symptomatic reaction noted at the time of the injection of Thorotrast, some untoward effects have been recorded.[12] These are of a systemic nature rather than those related to the local vascular tree, however.

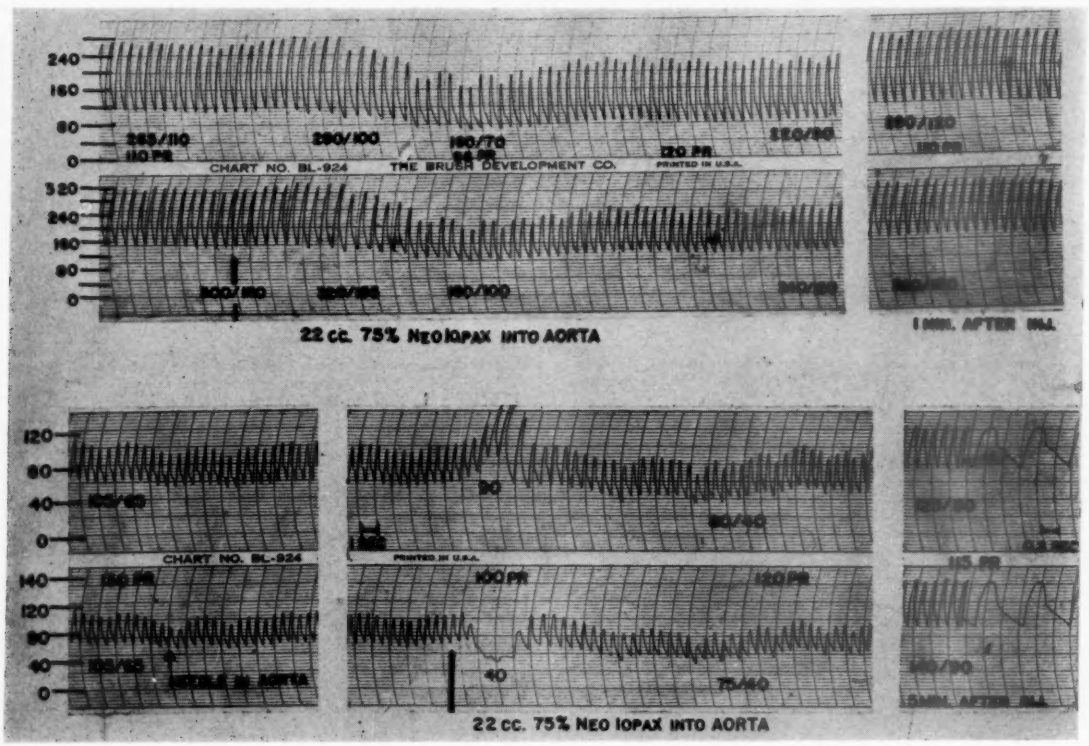


Fig. 3.—Records of the cardiovascular effects of injecting iodoxyl (Neo-Iopax) into the human abdominal aorta under local anesthesia. The first patient, a hypertensive man, developed a bradycardia and hypotension six seconds after beginning of injection. This period was followed by hypertension. The tachycardia was of short duration. The second patient, a normotensive woman, had a brachial hypertension and dampened femoral pressure during injection, followed by the usual phases of hypotension and hypertension.

On being injected into the blood stream, the colloidal suspension flocculates rapidly[9, 13] and is picked up within five minutes by the cells of the reticuloendothelial system.[13] In a short time, over two-thirds of the injected Thorotrast is stored in the liver.[14] This property made it popular for a time as an agent to permit roentgenologic visualization of the liver and spleen. However, it was found that elimination of the thorium was negligible and a check of gamma radiation by Geiger counter revealed that as much as 85 per cent of the activity of the Thorotrast originally injected was present in the liver four years later.[15] Late histopathologic changes were observed in animals and man;[13, 14, 16]

in one patient as long as eighteen years after injection.[17] Largely for these reasons, Thorotrast is not used widely in angiography.

2. Sodium iodide, when administered in large doses, may produce a clinical picture referred to as "iodism." This is characterized by nausea, excessive salivation, lacrimation, bronchitis, rash, and occasionally by delayed cerebral depression. Iodism has been decidedly rare, however, when the sodium iodide is injected into the aorta. Although a dose of 0.15 Gm. of iodide per kilogram of body weight has been said to be toxic when injected intravenously into animals,[18] a total of as much as 0.4 Gm. per kilogram of body weight has been injected into the aorta of the human being in three divided doses without serious consequences. This increased tolerance to iodides administered into the aorta, over that associated with the oral or intravenous route, has been noted previously by dos Santos.[19] In high concentrations, iodides may be very irritable in the vascular system, capable of producing endothelial damage and thrombosis,[20, 21] and may elicit a marked degree of vasomotor response.

3. Iodopyracet (Diodrast) has produced less evidence of iodism than sodium iodide when used for aortography. Generally, flushing of the face, urticaria, apprehension, dizziness, and nausea constitute the most severe symptoms. Occasionally, dyspnea, cyanosis, vomiting, and headache occur.[10] These symptoms are much less frequent and severe when the compound is injected into the aorta, than when it is given intravenously.

Iodopyracet (Diodrast) has appeared to be much less irritating to the vascular system than sodium iodide, as indicated by the lesser vasomotor reactions when it is injected into the aorta in comparable doses. However, large doses injected intravenously in dogs have caused profound effects terminated by death.[11] Intimal damage has been reported from the use of all the iodides[22-25] and even arterial thrombosis has occurred as a result of injection of iodopyracet in high concentrations.[23, 26]

4. Iodoxyl (Neo-Iopax) has produced about the same symptoms as iodopyracet, with the addition of dryness of the mouth. As with the previous compound, the effects are much less evident when the drug is introduced into the aorta. When given by the translumbar route, a not unpleasant warm sensation is noted inside the abdomen as the compound passes through the splanchnic arterial bed.

While the cardiovascular effects in dogs have appeared to be greater from iodoxyl (Neo-Iopax) than those observed with iodopyracet, the number of reported complications with the former has been less, owing, perhaps, to the fact that it has been used much less than iodopyracet in thoracic aortography, angiocardiography, and peripheral arteriography.

CONSIDERATION OF TECHNIQUES OF AORTOGRAPHY

As suggested by Castellanos and Pereiras,[27] aortography should be classified as direct and retrograde, and be subdivided further into the thoracic and abdominal routes, since the historical development and practical considerations are different.

A. Abdominal Aortography

1. Direct Route.—In 1929 dos Santos, the Portuguese urologist, reported before the Surgical Society of Paris his technique of translumbar aortography and clinical experiences with this means of visualizing the abdominal aorta, its branches, and the arteries of the lower extremities. His reports revealed that a high degree of success with little or no morbidity could be obtained with the use of iodides.[5-8] Osario, of Brazil, reported on 100 clinical cases, and described a few modifications of the dos Santos technique.[28] Impressed with the potentialities of the method, and having the opportunity of viewing a demonstration by dos Santos in this country, two American urologists, Doss and Nelson, independently explored the usefulness of aortography and reported on their clinical experiences.[29-37]

Subsequently, Wagner and his co-workers reported on the use of a simplified dos Santos technique in the study of vascular and urological disorders, and in the differential diagnosis of abdominal tumors.[38-40] Other reports have shown the safety and value of aortography in diagnosis of vascular lesions.[41-44] This technique has been used with safety in pregnant women to demonstrate placenta previa.[45-48] It was noted that iodopyracet (Diodrast) produced fewer reactions than sodium iodide.[47] Goodwin and co-workers,[49] Sante,[50] and Smith and associates[48, 51] have reported success with translumbar aortography in a large number of cases. They found the organic iodides quite satisfactory, with fewer reactions and an apparently wider margin of safety than that noted with sodium iodide.

In July, 1948, we began to perform translumbar aortography at the Presbyterian Hospital in New York, largely because of the interest of Dr. Arthur H. Blakemore in the surgical management of aortic aneurysms.[52-54] Consequently, our cases have been primarily those with vascular lesions. Although we performed aortograms on certain patients for the Department of Urology during 1950, the establishment of this technique in the Squier Urological X-Ray unit at the Presbyterian Hospital has been possible recently through the interest of Dr. George Cahill. Valuable modifications of the Wagner-dos Santos technique have been developed there by Dr. N. S. R. Maluf and Miss Cornelia McCoy.

It has been our practice to exclude patients with severe degrees of hepatic, renal, or cardiac disease, although extremes in age have been no deterrent. Preparation has consisted of giving the patient a light supper and 30 c.c. of castor oil the previous night. In the morning, a soapsuds enema is administered and food is withheld. Premedication is of the same type employed before a major surgical operation, being scopolamine hydrobromide and Demerol in appropriate doses.

In the x-ray room, the patient is placed prone on a table equipped with a Potter-Bucky grid. A control 14 by 17 inch film, using the rapid Potter-Bucky diaphragm, is exposed before induction of anesthesia. In general, we have employed 200 Ma. and 70 to 80 kv., with an exposure time of 0.3 second and a tube distance of 36 inches. This initial film has been of help in plotting the course of the aorta in patients with calcification of the vessels. In several instances,

the abdominal aorta was very tortuous and lay to the right of the midlumbar vertebrae. In such a case, it is best to aim the needle slightly higher than usual, so as to engage the aorta at the crus of the diaphragm where its position is constant.

In children, and in most of our adult patients, we have used intravenous Pentothal Sodium for anesthesia. However, because of anesthetic difficulties encountered in a few of the elderly patients, we have recently taken the lead of Dr. Maluf in relying on local infiltration, only. The skin and paravertebral area are anesthetized with 0.5 to 1 per cent procaine. When local anesthesia has been used, we have employed 20 c.c. of 75 per cent iodoxyl (Neo-Iopax) because of its minimal stimulation. In general, only a warm sensation is felt in the abdomen during the injection. Pain is noted only if extravasation occurs, and we feel that this sign is helpful in assuring us of a satisfactory injection.

When general anesthesia has been employed, we have used either 20 c.c. of 75 per cent iodoxyl (Neo-Iopax) or 10 to 20 c.c. of 80 per cent sodium iodide. Even under general anesthesia, the patient may stir and react to the stimulation from sodium iodide. In certain cases, we have injected 3 to 5 c.c. of 1 per cent procaine into the aorta a few minutes before injecting the sodium iodide, but little change in the reaction was noted. Consequently, we have not felt it wise to use sodium iodide with local anesthesia.

Technique.—The sterile set contains few special items (Fig. 4). Two medicine glasses are useful for holding sterile saline solution. We now place the contrast medium in a stainless steel cup so as to avoid confusing it with the saline solution. Standard needles and syringes are used for infiltration of the skin or fascia with 1 per cent procaine, whether local or general anesthesia is used. A Sise spinal introducer (Fig. 4, item *1*) is used to perforate the skin at a point 2 cm. below the twelfth lower rib margin, about 7 cm. to the left of the spinous processes. The malleable 16 cm., 18 gauge Wagner needle (Fig. 4, item *2*)* can be advanced without much resistance medially, anteriorly, and cephalad, much as is done when performing a splanchnic block (Fig. 5). After passing above or below the transverse process, the needle grazes the anterolateral aspect of the vertebral body. The patient may experience discomfort when the needle engages the vertebral fascia and periosteum. These structures may offer resistance similar to that of the aorta, but the absence of pulsatile thrust should differentiate them. About 2 cm. beyond vertebral contact the aorta can generally be felt with the needle point. Slight resistance similar to that of the dura mater is offered by the aortic wall. The needle is advanced into the lumen about 1 cm., and when the stylet is removed a trickle of blood runs down the shaft, rather than a pulsatile stream. We have used a steel 17 gauge needle with success, but prefer a malleable one which would bend in case the patient moved suddenly while the needle was in the aorta. A controlled Luer-Lok or Sana-Lok syringe and a connecting rubber or plastic tubing with stopcock and Luer-Lok adapter (Fig. 4, items *3* and *4*) are filled with saline solution and are fitted to the aortic needle when it is in position. The stopcock is turned to allow the blood to enter

*Sold by Geo. P. Pilling & Son, Co., Inc. Philadelphia, Pa.

the syringe. The pulsatile jet of red blood into the saline solution and the pressure against the plunger confirm the arterial nature of the blood. Barbotage should be carried out with ease, as resistance indicates poor position of the needle point.

When sodium iodide is employed, we have injected 10 c.c. of 30 per cent solution rapidly into the aorta and exposed the film just at the end of the injection. Examination of this aortogram (Fig. 7, *B*) will reveal the faint outline of the vessel in the region of the needle point. In this way, it has usually been possible to avoid injecting the 80 per cent iodide elsewhere than into the aorta.[21] In a few instances, we have withdrawn the needle and reinserted it properly, thus avoiding possibly severe consequences. When conditions are satisfactory, an additional dose of Pentothal Sodium is given and 10 to 20 c.c. of 80 per cent sodium iodide are injected by hand in two to five seconds (Fig. 6). Some authors believe the use of a pressure device necessary for good films.[7, 31, 35, 41] We have not felt this need, even when using the more viscid iodoxyl (Neo-Iopax). A pressure device might prove better with the more viscid 70 per cent Diodrast than the two needles, as used by some.

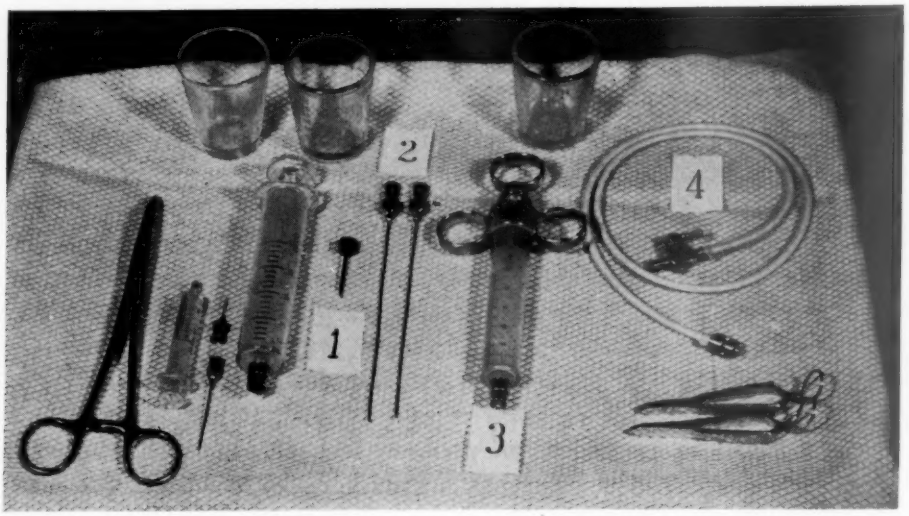


Fig. 4.—Tray containing equipment used in translumbar aortography: *1*, a spinal introducer used to perforate the skin; *2*, the malleable 16 cm. 18 gauge Wagner needles; *3*, a controlled Luer-Lok syringe; *4*, a connecting rubber (or plastic) tubing with stopcock and Luer-Lok attachments.

If the abdominal aorta or its primary visceral branches are to be visualized, the film is exposed immediately at the end of the injection. If the iliac or femoral arteries are to be shown, a delay of one to three seconds is advisable. For better visualization of the visceral arteries, tourniquets or pneumatic cuffs on the thighs have been recommended.[7, 45, 49, 50] Since most of our interest has been directed toward the aorta, we have rarely used them, and others have not thought them necessary.[35]

Immediately following the injection of the iodide, we have injected 30 c.c. of saline solution. We have inspected the aortogram before withdrawing the

needle, since it has been advantageous to repeat the injection in some patients, with some alteration in timing, position, or exposure factors.

Although the use of stereoscopic films in aortography has been reported previously,[7, 28] a technique has been developed by Dr. Maluf and Miss McCoy

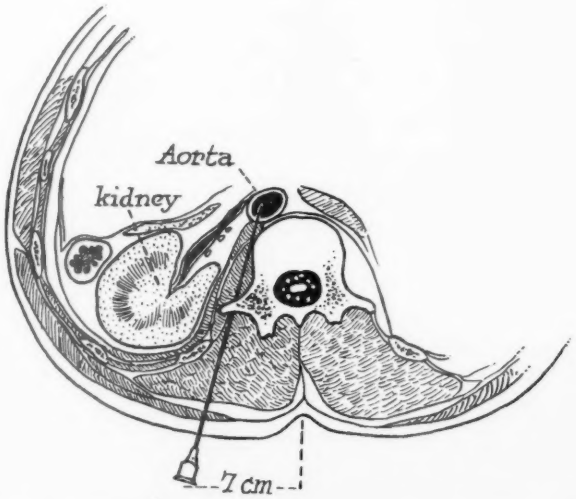
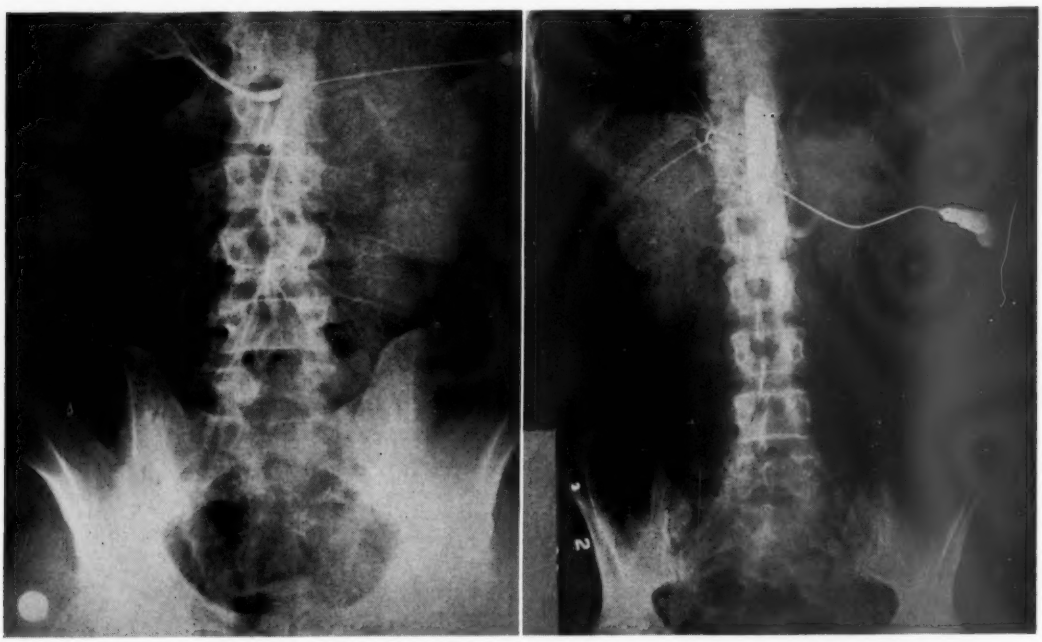


Fig. 5.—Diagrammatic cross section of the trunk indicating the position of the needle in translumbar aortography.

Fig. 6.—A patient is shown in the prone position on the x-ray table during the injection of the contrast medium for translumbar aortography.

which we have found very satisfactory. An exposure is made with identical timing during each of two injections of the contrast medium. During the several minutes between injections, the x-ray tube is shifted laterally four inches. A uniformity of density is possible by this technique, not easily achieved by exposure of two films during the same injection.

When iodoxyl (Neo-Iopax) is used, a test film has not been necessary. On one occasion, injection into the intestinal arteries was followed by no untoward effects (Fig. 7, *A*). Similar incidents with organic iodides have been reported without serious consequences,[48, 51] whereas death has followed such a procedure with sodium iodide.[21] A great difference has also been noted between the organic iodides and sodium iodide in regard to the sequelae from extravasation. In a few cases, iodoxyl (Neo-Iopax) has been injected outside the aorta. This was completely absorbed within an hour, with no ill effects nor symptoms other than trasient back pain. This has been noted by others.[48, 51] With sodium iodide, on the other hand, moderately severe symptoms occurred in three cases with extravasation (Fig. 7, *B*). Paresthesia and motor weakness have resulted from a chemical neuritis of the lumbar plexus, lasting from a few days to months.



A. *B.*

Fig. 7.—*A*, Translumbar aortogram made with 75 per cent iodoxyl (Neo-Iopax). The contrast medium has filled the superior mesenteric artery and colic arteries with no ill effects. *B*, Extravasation of 80 per cent sodium iodide. The aorta and renal and iliac arteries are visualized faintly. A moderately severe chemical neuritis of the lumbar plexus ensued. No ill effects have followed extravasation of iodoxyl (Neo-Iopax).

When the needle is withdrawn, a simple, dry dressing is applied. We have followed the practice of Nelson[35] and Wagner[39] in giving 1,000 c.c. of saline solution intravenously in patients who have had sodium iodide. Nelson had four cases of "iodism" prior to adopting the technique of saline solution to hasten excretion of the iodide ion. We have not found it necessary to use the infusion in patients who have had iodoxyl (Neo-Iopax).

We have studied 48 patients from the Surgical Service, and 7 from the Urological Service of the Presbyterian Hospital (Table I). Of the latter, four

had hypertension and it was hoped that aortography could differentiate a renal lesion from essential hypertension. The remaining three had horseshoe kidney or renal malignancy.

TABLE I. AORTOGRAMS FROM THE SURGICAL SERVICE OF PRESBYTERIAN HOSPITAL

DIAGNOSIS	NO. OF PATIENTS	NO. OF STUDIES	SEX		AGE RANGE (YEARS)
			MALE	FEMALE	
A. Direct Abdominal Route					
Aneurysm of aorta	26	34	22	4	30-79
Suspected aneurysm	12	12	6	6	37-56
Normal	7	7	4	3	42-56
Extrinsic tumor	5	5	2	3	37-50
Peripheral arterial lesions	10	14	6	4	3-57
Embolism	1	1	0	1	28
Occlusive disease	5	6	3	2	43-57
Arteriovenous fistula	4	7	3	1	3-54
Urological	7	7	5	2	40-56
Total	55	67	40	15	3-79
B. Retrograde Thoracic Route					
Via ulnar artery					
High aortic obstruction	1	1	1	0	47
Aneurysm	2	2	2	0	54-60
Via carotid artery					
Coarctation	8	8	6	2	8-29
Anomaly of aortic arch	1	1	1	0	10 mo.
Postoperative tetralogy	1	1	0	1	5
Truncus arteriosus communis	1	1	0	1	21
Aneurysm, arch	1	1	1	0	46
Total	15	15	11	4	10 mo.-60

Of the 48 cases, there were 34 studies of 26 patients with aneurysms of the abdominal aorta. Of these, all but two were arteriosclerotic, usually with aneurysms of the fusiform type (Fig. 8, *A*). A few of the arteriosclerotic aneurysms were saccular (Fig. 8, *B*), as were both of the syphilitic aneurysms (Fig. 8, *C*). Only four of these patients were women, and the age of the aneurysm group ranged from 30 to 79 years, with 8 over 70 years.

Of 12 patients referred to us because of suspected aortic aneurysms, 7 were found to have no abnormalities of the vascular tree. The remaining 5 patients were found to have a deviation of the aorta indicative of extrinsic pressure (Fig. 9). In such cases the lumen is generally of uniform caliber and there is a buckling of the iliac artery on the side of the aortic convexity. The opposite iliac artery has little or no tortuosity, a picture unlike the bilateral tortuosity observed with arteriosclerosis. We have confirmed this mechanical effect in the animal laboratory. Among the 5 patients, 2 had carcinoma of the pancreas, 1 had a pancreatic cyst, and 2 had retroperitoneal metastases. In at least 2 of these, the physical signs were completely compatible with aneurysm.

Peripheral arterial lesions were studied in 10 patients. In 1, an external iliac embolus had presumably caused retrograde thrombosis, so that no collateral channels could re-establish flow in the superficial femoral artery (Fig. 10). Lumbar sympathectomy rather than thrombectomy was performed. Several patients with arteriosclerosis obliterans were studied to determine the level of

A. *B.* *C.*

Fig. 8.—*A*, Aortogram showing a typical fusiform arteriosclerotic aneurysm of the abdominal aorta. Note the deviation of the aorta to the left in the lower lumbar region.

B, Aortogram of a large saccular arteriosclerotic aneurysm of the abdominal aorta. Note the marked deviation of the lower aorta to the right in this case. The aneurysm presented clinically as a pulsatile mass in the right epigastrium.

C, Aortogram of a saccular syphilitic aneurysm of the abdominal aorta. In this type of aneurysm, the sac is irregular and appears above the renal arteries, in contrast to the arteriosclerotic aneurysms.

occlusion. Of the 4 patients with arteriovenous fistulas, 2 had congenital fistulas, involving branches from the iliac artery. Of the traumatic cases, 1 involved the common femoral vessels, and 1 the visceral vessels of the upper abdomen.

Dr. Maluf of the Urological Service has performed over 40 aortograms within a few months, preferring local anesthesia and iodoxyl (Neo-Iopax) in most cases. Thorotrast was used in a few with no advantage observed, and with the presumptive disadvantages described previously.

Fig. 9.

Fig. 10.

Fig. 9.—Aortogram showing characteristic deviation of aorta produced by an extrinsic mass. Note the angulation of the iliac artery only on the side of aortic convexity. With a tortuous arteriosclerotic aorta, both iliac arteries are angulated in a similar manner.

Fig. 10.—Aortogram of a young woman following embolization from a fibrillating heart to the right iliac artery. The collateral circulation formed by the hypogastric artery re-enters the profunda femoris artery. The superficial femoral artery on the right does not fill with the contrast medium.

In over 100 aortographies performed at Presbyterian Hospital, there has been no mortality. The literature is confusing as to the number of mortalities occurring among over 2,000 cases of dos Santos, but in any event, there were either none or very few.[41] There were no mortalities among the hundred cases of Osario,[28] nor among subsequent series[29-37, 41-51] with the exception of that of Wagner.[21] Smith and his colleagues have performed over 700 aortographies using the organic iodides with no untoward sequelae.[48]

The misleading results of certain experimental studies[55] in which toxic doses of iodides were injected into dogs by the translumbar approach, with resultant hemorrhage or death, may have deterred many from using this valuable diagnostic aid. The needle hole in the human aorta readily seals itself because of the elasticity and thickness of the wall. Subsequently, it may be difficult to detect the site of puncture. Studies of the aorta at this site have

been carried out.[38, 51] There have been no cases in which hemorrhage was observed, and the actual minimal extent of the hematoma has been reported.[38, 51] Puncture through an atheromatous plaque is but rarely the cause of complication. Lilly[56] describes the case of a man who had embolization of a plaque during aortography. This was proved by embolectomy, which failed to save the leg.

The morbidity has appeared to be minimal following injection of organic iodides. With the use of sodium iodide, however, we have had 2 patients with transient encephalopathy and 3 with peripheral neuritis subsequent to extravasation. Iodism and nephritis have been reported following injection of sodium iodide.[35, 57] We have not performed any test for sensitivity to iodides, when carrying out translumbar aortography, although we do so before angiocardiography. Scott[20] has analyzed angiography deaths from iodide sensitivity and raises the question as to the actual value of such tests.

In summary, it would appear that in the interests of the patient, we should recommend the wider use of local anesthesia and of the organic iodides, even though the opacification is less than that observed with sodium iodide. Stereoscopic films are of great value in certain cases, but require two injections for best results. To date, the rapid exposure devices available commercially in America do not seem adequate.[49, 51] It is now possible to obtain synchronous serial films in two planes,[58-60] and we hope this development will someday be applicable to abdominal aortography. Our few attempts to obtain lateral aortograms by simultaneous exposure with a portable machine have been unsuccessful. It is expected that translumbar aortography will be of increasing use to the vascular surgeon.

2. Retrograde Route.—In 1932, Saito and Kamikawa[61] reported their experiences with a successful technique of visualization of the major vessels by injection of an emulsion of iodized oil retrograde into peripheral arteries or a collateral branch. They did not mention visualization of the aorta, however.

In 1937, Castellanos and his associates obtained an abdominal aortogram by retrograde injection via needle in the femoral artery, in an attempt to obtain a phlebogram by direct puncture of the femoral vein.[27] This case was reported in 1939. Previous and subsequent reports in the Cuban and American medical literature attest to extensive and original work in angiocardiography[62] and retrograde aortography[63-65] by Castellanos and his colleagues. Also from Cuba, Fariñas developed a modification of the technique of Castellanos and associates which he reported before the American Roentgen Ray Society in 1940. His subsequent publications[66-69] described the use of a ureteral or rubber catheter introduced up the aorta through a trocar in the femoral artery. Tourniquets were applied to the thighs, and 70 per cent iodopyracet (Diodrast) was injected by a special apparatus delivering 15 lbs. of pressure.

The further use of this technique has been reported by Levy and Llambés,[70] Freeman and Miller,[26] Goodwin and associates,[49] and Helmsworth and associates.[71] The practical disadvantages have kept this method from becoming popu-

lar. It requires operative exposure and incision of a major peripheral artery. The dangers of spasm and reduction of blood flow into the extremity because of the catheter itself may be of importance in elderly arteriosclerotic patients. It would be easier to dislodge an aortic atheromatous plaque during manipulation of the catheter than by direct needle puncture. Such a complication has occurred in our series of retrograde ulnar aortograms with tragic consequences. The possible advantage of being able to inject the contrast medium at a desired level has not offset the disadvantages.[49] Since we have not found any occasion in which the translumbar method has been unsatisfactory, we have not made use of the retrograde method for visualization of the abdominal aorta.

B. Thoracic Aortography

Techniques for thoracic aortography have been associated with more dangers than those for abdominal aortography. Consequently, an effort should be made to opacify the thoracic aorta, preferably in the right posterior oblique or left anterior oblique position, by means of angiocardiography before considering aortography. Most of our failures with angiocardiography have been in large adults with aortic dilatation or aneurysm, or in children with anomalies of the aortic arch. The dilution of the contrast medium by passage through the lungs is at times sufficient to prevent sharp definition of the vascular tree in the upper thorax. Overlying soft tissue shadows and the varying contrasts of the pulmonary structures further complicate roentgenologic interpretation.

1. *Direct Route.*—In 1936, Nuvoli[72] is said to have visualized the thoracic aorta by insertion of a needle directly into the vessel through the anterior chest. Subsequently, Blakemore[1] visualized the abdominal and thoracic aorta at operation, coincident with electrothermic coagulation in the treatment of aortic aneurysms. Iodopyracet (Diodrast) was injected rapidly through the large needle used for insertion of fine insulated wire. A film was exposed in the operating room using a portable x-ray machine. While developing this technique of therapy,[1, 52, 53] visualization was used to gauge the degree of obliteration of the sac. The direct needle approach was considered to have caused a fatal hemorrhage in one patient,[73] and has been abandoned for visualization of the thoracic aorta at Presbyterian Hospital. It was thought that the large caliber of the needle and a severe lipemia in the patient contributed to the fatality, however.

In 1945, Radner[74] reported a transsternal technique. Thorotrast was injected rapidly in an effort to visualize the coronary arteries in 5 patients. Complications occurred in 2 instances, but there were no deaths. This author had abandoned the direct approach for a retrograde technique.[75]

From Mexico have come reports by Gomez del Campo and Menenses Hoyos[76, 77] on a technique by which an 18 gauge needle is introduced with Pentothal Sodium or local anesthesia, through the left second intercostal space, into the thoracic aorta. Thirty c.c. of 70 per cent iodopyracet (Diodrast) were rapidly injected with no serious sequelae in 4 patients.

It would appear that the theoretical dangers from bleeding are greater when the thoracic aorta is punctured, because of anatomical differences in the fascial and muscular planes of the chest and abdomen. Such fears may be unfounded, but the direct technique has not gained favor in visualizing the thoracic aorta.

2. *Retrograde Route.*—In 1937, Castellanos and Pereiras[27] obtained a retrograde visualization of the thoracic aorta by injecting a contrast medium through a needle inserted into the axillary artery. Subsequent successful studies were carried out via the brachial artery.[27, 63] Several reports from Sweden in 1948 indicated a preference for use of a ureteral catheter introduced into the thoracic aorta by way of the radial artery.[75, 78, 79] Brodén and his colleagues have taken serial films in two planes, and have found it unnecessary to sacrifice the radial artery.[78] Freeman and Miller[26] reported on a case studied in 1947, and noted difficulty in manipulating the catheter into proper position. This patient showed cerebral symptoms following injection of 70 per cent iodopyracet (Diodrast). The same authors also noted difficulties in techniques making use of a catheter into the brachial artery, and subsequently Freeman and colleagues reported the use of a needle in the exposed left common carotid artery of 15 patients wtih coaretation.[80, 81, 82] Independently, Burford and associates presented a very similar technique.[20, 83, 84] Twenty-three patients with congenital anomalies were studied with no deaths nor untoward effects. Excellent visualization has been possible by this technique.

Jönsson has performed successful retrograde visualization of the thoracic aorta in 10 cases by percutaneous insertion of a special needle into the common carotid artery.[85] He injected 40 to 80 c.c. of 50 per cent iodopyracet (Diodrast) by a pressure device and obtained seriograms in two planes. He advocated use of heparin and penicillin following each examination.

Although Gross[86] has relied on a catheter introduced via the axillary artery and Crafoord[87] and Helmsworth and associates[71] have preferred a catheter into the brachial or ulnar collateral arteries, most satisfactory results appear to have been obtained via the common carotid artery.

We made use of a polyethylene catheter via the ulnar artery in 1949 and 1950, but since early 1950, we have generally preferred the left common carotid artery.

Technique: The patient is prepared simply by withholding food for twelve hours and administering premedication of scopolamine and Demerol an hour before operation. Although Freeman has had success with local anesthesia in the carotid technique,[82] we have preferred a general inhalation anesthesia. Local anesthesia has been adequate for the method utilizing the ulnar artery.

In the operating room, the usual surgical instruments for exposing a peripheral artery are required. Few special items are needed (Fig. 11). We have used 70 per cent iodopyracet (Diodrast) (Fig. 11, item *1*), but have diluted it with saline solution to 50 per cent or less. A Robb 50 c.c. eccentric Luer-Lok syringe (Fig. 11, item *2*) facilitates rapid injection of the contrast medium. The Robb needle and cannula (Fig. 11, item *3*), a Lindemann needle,

or a venous cannula have been used occasionally instead of the thin-walled pure polyethylene catheters* of various diameters and lengths (Fig. 11, items *4* and *5*). The longer one has been required for the ulnar approach.

ULNAR ARTERY.—For exposure of the right ulnar artery, an area below the crease of the antecubital space, medial to the midline, is infiltrated with one per cent procaine. Through a slightly oblique incision, the bifurcation of the brachial artery is readily identified and mobilized. The first centimeter or two of the ulnar artery is isolated by loops of cotton umbilical tape. A small incision is made into the vessel and the polyethylene catheter which has been filled with saline solution and heparin is advanced to the level of the first rib (Fig. 12, *A* and *B*). At this point, it is often difficult to advance the catheter.

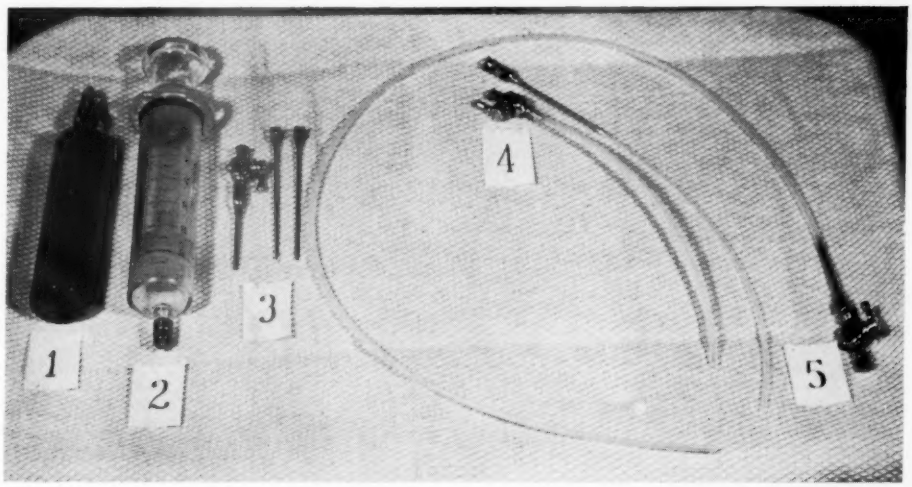


Fig. 11.—Tray containing equipment used in retrograde visualization of the thoracic aorta: *1*, a vial of contrast medium (either iodopyracet [Diodrast] or iodoxyl [Neo-Iopax] has been considered satisfactory, after dilution to 50 per cent concentration); *2*, a 50 c.c. eccentric Luer-Lok Robb syringe; *3*, a 12 gauge Robb cannula with the needle and blunt stylet: *4*, Polyethylene catheters used in the retrograde carotid approach (the short catheter with the stopcock measures 0.085 inch, internal diameter, and 0.135 inch, external diameter. The other two catheters measure 0.062 inch internal diameter and 0.094 inch external diameter); *5*, long catheter found most satisfactory for the ulnar approach.

It has been found helpful to move the patient to the fluoroscopic table, and manipulate the catheter under direct vision, after filling it with contrast medium. When the tip of the catheter lies in the desired position in the aorta, the patient is placed in the correct position. In adults we have introduced 20 to 40 c.c. of 50 per cent iodopyracet (Diodrast) in 0.5 to 1.5 seconds. While this is being injected an assistant occludes the common carotid arteries by digital pressure. The catheter is then refilled with saline solution and heparin, or is attached to a continuous pressure infusion of saline solution.

The x-ray film is exposed as the last few cubic centimeters of iodopyracet (Diodrast) are being injected. We have used 400 Ma., and 80 to 90 Kv. with an exposure time of 1/30 or 1/40 second, and a tube distance of 36 inches. A stationary Lysholm grid is always used to improve definition of the vessels. If the film is not satisfactory, additional injections may be carried out.

*Obtained from Surprenant Manufacturing Company, Clinton, Mass.

The patient then is returned to the minor surgery suite where infiltration of additional procaine may be needed. Bulldog serrefines are placed proximal and distal to the incision in the ulnar artery after the catheter is removed and the lumen flushed free of any possible thrombus. A few sutures of braided 00000 arterial silk are usually placed, although in one elderly man the ligation of the ulnar artery had no consequences. Simple closure of the wound and instillation of 100,000 units of penicillin complete the procedure.

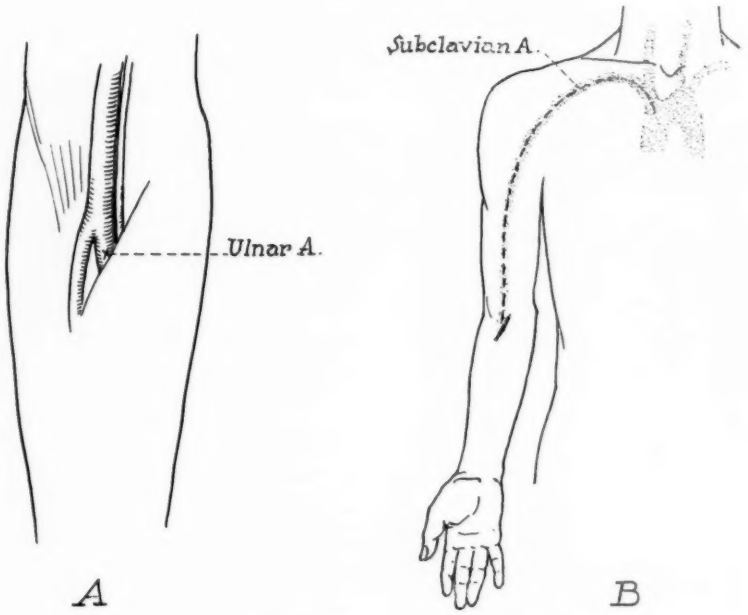


Fig. 12.—*A*, Site of introduction of the catheter into the ulnar artery.
B, Route of the catheter as it is advanced into the aorta under fluoroscopic control. Difficulty is often encountered at the level of the first rib.

Carotid Artery.—For exposure of the left common carotid artery, the left shoulder is elevated by a thin sandbag pillow. A 5 cm. incision is made 1 cm. above, and parallel to, the midportion of the clavicle (Fig. 13, *A*). The platysma is divided and the sternocleidomastoid muscle is retracted medially. The carotid sheath is entered and the internal jugular vein retracted laterally (Fig. 13, *B*). A 5 cm. length of common carotid artery is easily mobilized and a segment isolated by cotton umbilical tapes. Originally, the polyethylene catheter was tied into the artery after introducing it through a small incision (Fig. 13, *C*). Subsequently, we have simply tightened the loops during injection, and controlled the minimal leak about the catheter with the gloved fingers. In this way, blood flow is occluded for but a few minutes during injection.

Initially, we took the patient to the x-ray room in order to get the films, using the same exposure factors as employed with the ulnar technique. Being dissatisfied with this procedure because of the lengthy period of carotid occlusion and the threat to sterility, we have made use of the portable x-ray machine in the operating room with satisfactory results.

In children we have used 8 to 25 c.c. of 35 to 50 per cent iodopyracet (Diodrast), and in adults, we have found 20 to 40 c.c. of 50 per cent concentration best. Exposure is made as the last few cubic centimeters are rapidly injected, with digital occlusion of the contralateral carotid artery. Repeated injections may be necessary, or desired in another position.

When the study is completed, the catheter is withdrawn, and the loops tightened after free escape of blood. It is advisable to allow flow to come from

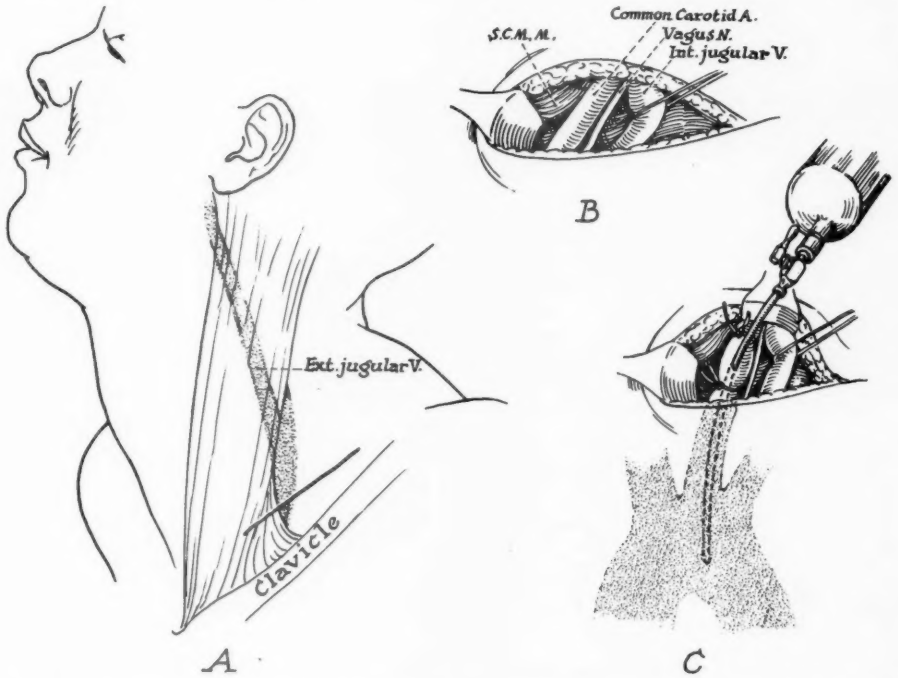


Fig. 13.—*A*, Diagram to show position of the patient, site of incision, and position of the structures encountered in retrograde carotid aortography.

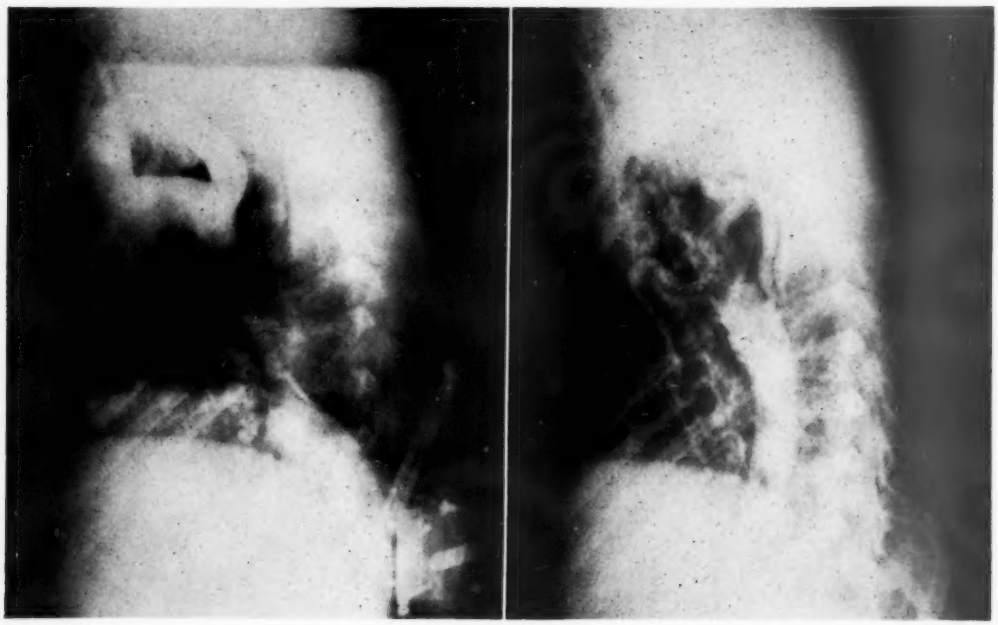
B, Relative position of the common carotid artery, vagus nerve, and internal jugular vein.

C, Catheter is shown being advanced into the aorta. Tip may be manipulated so as to lie in the ascending or descending portion of the arch.

the distal portion of the carotid artery first, to prevent any thrombus passing into the cerebral circulation. The arterial incision is repaired with a continuous suture of 00000 braided arterial silk, and circulation thus restored. The platysma muscle and skin are approximated finally.

Since early in 1949, we have performed retrograde aortography via the ulnar artery in 3 patients, and via the carotid artery in 12 patients (Table I). We elected to use the ulnar artery in the older group, fearing the consequences of carotid occlusion. In none of these 3 cases was the visualization considered good, and our most severe complication occurred in this group. The patients studied via the carotid artery were young, with one exception, and except for this case, all had congenital anomalies of the great vessels. Most had coarctation of the aorta, which is often poorly demonstrated by angiocardiography. Films exposed one-half second apart, or less, reveal the stenosis as well as the retro-

grade filling of the distal aorta through the dilated intercostal arteries (Fig. 14, *A* and *B*). In one patient with persistent hypertension following excision of a coarctation and subclavio-aortic anastomosis, the coronary arteries were well demonstrated, as were the aortic valves (Fig. 15, *A* and *B*). These structures were well visualized in several other cases in which the catheter was well advanced into the ascending arch. No untoward signs nor symptoms were observed in these patients. This technique was of practical help in a patient with tetralogy of Fallot who had had return of severe cyanosis sometime following a Blalock procedure. The right subclavian artery which had been



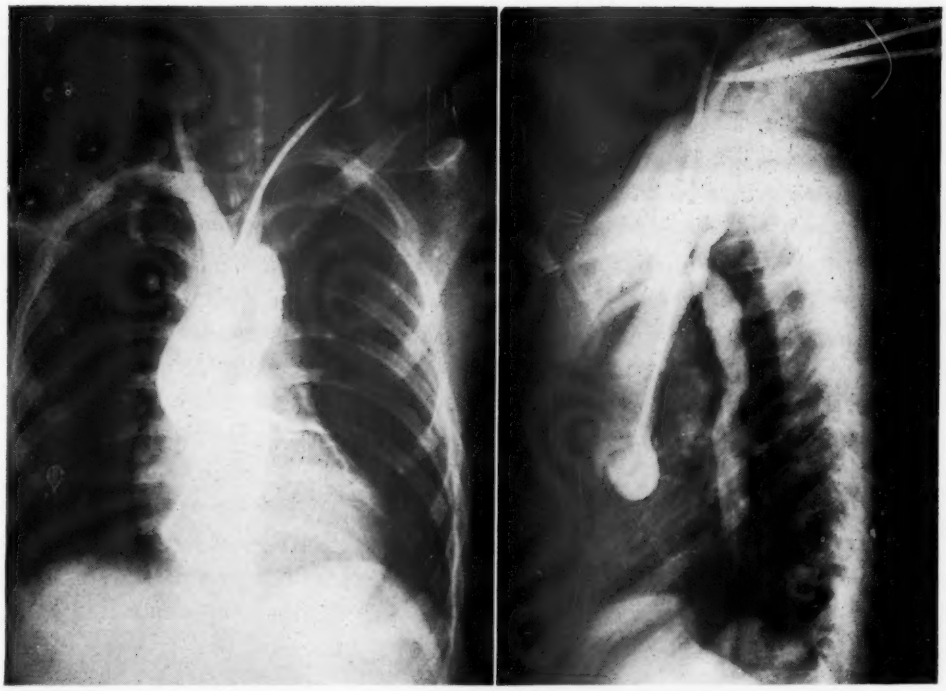
A *B*.

Fig. 14.—*A*, Retrograde carotid aortogram obtained in the right posterior oblique position clearly outlines an almost complete coarctation of the aorta. A thin line of contrast medium issuing from the middle of the proximal aorta indicates a tiny opening. The dilated left carotid and subclavian arteries are well shown.

B, Picture of the same patient obtained less than 0.5 second later. The contrast medium is shown entering the slightly dilated aorta distal to the coarctation by way of the dilated, tortuous, intercostal arteries.

anastomosed to the pulmonary artery was found to be occluded by thrombosis. Definite information was obtained in a 10-month-old boy with an anomaly of the aortic arch (Fig. 16). By comparing the aortogram obtained in two projections with comparable esophagrams, it was apparent that there was a left posterior aortic arch with constriction of the trachea and esophagus resulting from a fibrous band to an anterior left subclavian artery.

There was a related fatality in the group studied via the ulnar artery. This 47-year-old man was suspected of having a high aortic obstruction, and a previous angiocardiogram was of no diagnostic help. A sudden severe pain in the left side of the head occurred as the polyethylene catheter was advanced from the left subclavian artery. Presumably, an atheromatous plaque was



A. *B.*

Fig. 15.—*A*, Retrograde carotid aortogram obtained by polyethylene catheter in the anteroposterior position. The patient had a subclavio-aortic repair for coarctation of the aorta one and one-half years previously. Note the relative narrowing of the subclavian artery. The right internal mammary artery is still dilated and tortuous. The coronary arteries and aortic valves are well demonstrated.

B, A picture of the same patient in the right lateral position shows the same structures in another projection. Note the bulging into the left ventricle of the aortic valves as a result of the force of the injection. The coronary artery is well shown.

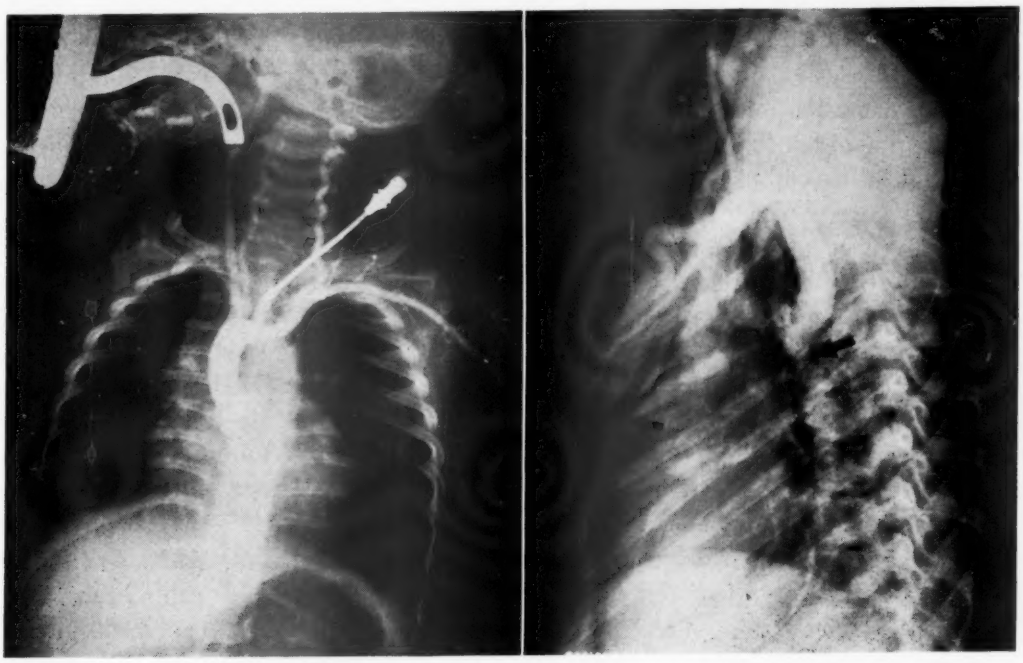


Fig. 16. Fig. 17.

Fig. 16.—Retrograde carotid aortogram of an infant 10 months of age. A constriction of the trachea and esophagus resulted from a residual fibrous band between the large posterior aortic arch and the narrow anterior arch which gave origin to the left common carotid and subclavian arteries. Note the aortic valves and coronary artery.

Fig. 17.—Retrograde carotid aortogram obtained by catheter with the patient in the right posterior oblique position. The arrows mark the pneumomediastinum and the site of a moderate coarctation of the aorta. The left subclavian and internal mammary arteries are very dilated.

pushed ahead of the catheter and passed into the left carotid artery. During the injection of 50 per cent iodopyracet (Diodrast) a convulsion occurred despite digital occlusion of the carotid arteries. A right hemiplegia and facial weakness was noted shortly thereafter. The patient died two days later.

Transient but immediate aphasia and contralateral hemiplegia occurred in two patients in whom the carotid approach was used. One was a boy of 8 years with coarctation of the aorta, and the other a man of 46 years, who had had partial occlusion and wiring with electrothermic coagulation of a syphilitic aneurysm of the decending thoracic aorta. The aphasia cleared in a few weeks but the hemiplagia remained for months. There was still residual weakness in this man, over six months after the aortogram.

Pneumomediastinum was noted in one patient with coarctation, but proved to be of no consequence (Fig. 17). In this boy, and in eleven other patients, the recovery was completely uneventful. No extravasations occurred and very successful visualization was accomplished in all the cases studied via the carotid artery.

COMMENT

We are not happy with our experiences in retrograde visualization of the thoracic aorta, but we are not yet anxious to explore further direct needle puncture. In none of our cases studied via the ulnar artery was the visualization good, and yet a polyethylene catheter with an outside diameter of 0.094 inch and an inside diameter of 0.062 inch was used. We had difficulty in positioning the tip of the catheter as noted by Freeman and Miller.[26] Fatalities associated with the use of a similar technique have been reported by Helmsworth and associates,[71] and by Glover.[88]

The complications noted in two cases studied via the carotid artery might have been avoided had we used only a needle instead of a catheter. We thought a small local thrombus was at fault in each patient, rather than cerebral ischemia resulting from carotid occlusion. The convulsive reaction to a strong solution of iodopyracet (Diodrast) has been noted by others,[23, 26, 71, 88] and we feel, as others do, that the concentration should not exceed 50 per cent.[23] These occurrences emphasize the fact that no visualization should be done without a reasonable purpose, and that angiocardiography should be relied upon whenever possible rather than retrograde routes, even though the definition is not as good. Experience in interpretation will often obviate the need for extreme contrast. Further impovements in x-ray equipment used for fluoroscopy and rapid serial exposures will, no doubt, make angiocardiography more useful with lesions of the aorta.

Visualization of the coronary arteries has been accomplished by others. Rousthöi[89] demonstrated the coronary arteries of dogs and rabbits in 1933. Radner[74] reported his efforts with a transsternal route in 5 cases, employing 20 to 30 c.c. of Thorotrast. Grossman[90] opacified the coronary arteries in dogs, using 70 per cent iodopyracet (Diodrast) through ureteral catheters introduced into the aorta via the common carotid artery. Jönsson,[91] and Pearl and associates[92-94] have made use of a catheter introduced via the radial artery to outline

the coronary arteries in man. McAllister,[95, 96] working with Leighninger and Beck, visualized the coronary veins and the autogenous vein graft from the thoracic aorta to the coronary sinus in his experiments on revascularization of the heart. A catheter was advanced to the proper level via the femoral artery, and iodopyracet (Diodrast) was injected rapidly. With an increasing number of successful operations of this type in human beings suffering from coronary insufficiency, it has seemed worth while having available a satisfactory technique for visualization of the coronary arterial tree. In none of the human beings in whom these arteries were seen was there noted any untoward effect of the contrast medium on the heart.

It becomes evident that as new vascular surgical techniques appear, permitting additional corrective procedures on the great vessels and even on structures inside the heart, these special techniques for visualization will have to keep pace.

SUMMARY

The technique for direct translumbar aortography was reported in 1929 by the Portuguese urologist, dos Santos. Until recently it was rarely used by the vascular surgeon. The dos Santos technique has remained essentially unchanged to the present time. The variations have been in the choice of anesthetic, in the use of leg tourniquets and pressure injection devices, and in the contrast medium. While we have had success with the Wagner modification, making use of Pentothal Sodium anesthesia and injection of sodium iodide by hand syringe, at present we see greater advantages and safety in a technique employing local anesthesia and an organic iodide. Among 55 patients studied by the Surgical Service and over 40 by the Urological Service, there were no fatalities. Transient encephalopathy was noted in 2 patients and chemical neuritis in 3, all of whom received 80 per cent sodium iodide.

Retrograde abdominal aortography appears to have no advantages over the translumbar method and there are definite practical disadvantages.

In visualizing the thoracic aorta, the direct approach has been far less popular or successful than the retrograde route. The organic iodide compounds have been most satisfactory, being injected via needle or catheter introduced into the arteries of the upper extremity or the common carotid artery. Poor visualization and one related fatality were experienced in 3 cases having iodopyracet (Diodrast) injected through a catheter into the thoracic aorta via the ulnar artery. Excellent visualization but 2 serious complications resulted from the use of a catheter into the left common carotid artery of 12 patients.

Experimental studies in dogs, and some of the cases in human beings, indicated a consistent pattern of vasomotor response to intra-aortic injection of four different contrast media. There was a considerable difference in the degree of the cardiovascular effects with the various agents tested, sodium iodide causing the greatest changes.

I wish to acknowledge the help and interest of Dr. George H. Humphreys, and Dr. Arthur Blakemore and of the Chest Residents of the Department of Surgery. The development of these techniques was possible largely through the assistance of Dr. Robert Ball, formerly of the Department of Radiology. The technical aid of Dr. H. Fitzpatrick, Dr. S. Weissman, Dr. J. Mandell, and Dr. N. S. R. Maluf was invaluable.

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REGIONAL HEPARINIZATION AFTER THROMBOENDARTERECTOMY IN THE TREATMENT OF OBLITERATIVE ARTERIAL DISEASE

A Preliminary Report Based on Twelve Cases

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REGIONAL heparinization, first described by Murray and Best,[1] has been found to be of increasing importance in vascular surgery. Its use after removal of emboli and after arterial repair following injury or excision of an aneurysm was described by Freeman, Wylie, and Gilfillan.[2] Wylie, Gardner, Johansen, and McCorkle[3] have reported on its use in experimental animals. More recently Blakemore[4] has reported using regional heparinization after the partial ligation of the abdominal aorta in the treatment of aneurysms of this structure. Blakemore and Fitzpatrick[5] have also described the use of regional heparinization after insertion of a vein graft to bridge the gap between the splenic vein and the left renal vein or vena cava in the treatment of portal hypertension. The present report deals with its use after thromboendarterectomy in the treatment of obliterative arterial disease. Although our experience with regional heparinization in the treatment of this condition has not been extensive, the results in the twelve cases here reported have sometimes been so gratifying that further use of this technique will probably be made. Emphasis in this report will be placed upon the failures, and especial attention will be drawn to our errors, both in technique and in the selection of patients, which may have contributed to the failures. It is hoped that by a frank appraisal of this procedure, its place in the treatment of obliterative arterial disease can be established.

Thromboendarterectomy was first described by dos Santos[6] at the Congress of London in 1947. Arnulf,[7] in his classical monograph on surgery of arteries, published in 1950, has given an excellent review of the experience of the French surgeons in the performance of this operation. This operation is possible, as he has pointed out, due to the fact that a line of cleavage is present between the thrombotic material and the viable arterial wall. This line of cleavage apparently is just within the internal elastic membrane. Following removal of the thrombus, plus the intima and part of the media, sufficient viable arterial wall remains to permit closure with restoration of the lumen of the artery.

To prevent the recurrence of thrombosis, generalized anticoagulant therapy has heretofore been used. The dangers of hemorrhage at the operative

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site or elsewhere with the use of generalized anticoagulant therapy have been well recognized. Wylie and his associates[3] have noted the trouble from bleeding from the operative wounds in their heparinized animals and have reported three instances of massive hemorrhage, one of which was fatal, in patients receiving adequate systemic doses of heparin after embolectomy. It was felt that the use of regional heparinization, by injecting heparin solution into the artery directly above the zone from which the intima had been removed, might prevent the reformation of the thrombus without at the same time running the risk of hemorrhage from systemic heparinization.

TECHNIQUE

The following technique has been found to be satisfactory:

Radiographic visualization of the arterial system is indispensable, since the presence of a patent artery of suitable size distal to the occlusion is essential. Retrograde arteriography,[8] with the use of the Valsalva maneuver,[9] has been found most useful in visualizing the aorta and its major branches. Direct aortography,[10] has been used in two cases. Due to the complications from the 80 per cent sodium iodide in these patients, we have subsequently used only 70 per cent Diodrast.

Adequate exposure of the involved artery is essential, and the incision should be so placed that the involved artery can be adequately controlled well above and well below the zone of obstruction. Only by wide exposure can the dangers and difficulties of this procedure be avoided. The failures in three out of the first four cases reported in Table I may well have been due to inadequate exposure.

It is important to realize that thromboendarterectomy is generally indicated in patients who have extensive degenerative arterial disease. Even though the area of occlusion is limited, there are usually atheromatous changes in the vessel above and below the point of obstruction. The main vessels above and below the zone of obstruction should be temporarily occluded by suitable clamps and the branches should be controlled by means of rubber bands. The clamps which are used to occlude the main artery must be placed in such a way as not to crush the vessel wall with possible dislodgment of an atheromatous plaque. Although thromboendarterectomy can be performed through multiple transverse incisions, as originally reported by dos Santos, it is our belief that a longitudinal incision of the arterial wall is the procedure of choice. This incision should extend well beyond the limits of the thrombotic area and should be made with the scalpel down into the occluding material.

When the vessel is opened throughout its entire length, a lumen will become apparent at either end of the zone of obstruction. A line of cleavage will generally be found readily, but as much viable vessel wall should be preserved as possible. By means of a blunt dissector, the occluding mass, which has been termed a "sequestrum" by Arnulf,[7] can generally be separated. At the origin of branches of the main artery the atheromatous thickening disappears, and at these points the lining is simply cut across with fine scissors.

It has been found useful to divide the vessel lining in an oblique fashion at the proximal and distal ends of the atheromatous plaque, in order to prevent, if possible, too abrupt an ending of the thickened vessel wall. This step is particularly important at the lower end.

It has been deemed advisable to tack down the lining of the artery at both ends with interrupted stitches of 00000 Deknatel braided silk, in order to prevent the development of a dissecting aneurysm with subsequent thrombosis of the vessel. The needle enters the lumen of the artery through the thickened lining and passes out again through the denuded portion. The stitch can then be tied on the outside of the vessel. Three or four such sutures have generally been used. Back-bleeding from the distal end of the artery and from the branches can readily be observed upon temporary release of the occluding clamps or bands. The denuded portion is then irrigated with heparin solution, 50 mg. in 250 c.c. of saline solution, and the vessel is closed. A continuous over-and-over stitch with 00000 Deknatel braided silk has been found to be satisfactory. Since the intima has been removed the mattress suture generally used in the surgery of normal arteries is not necessary.

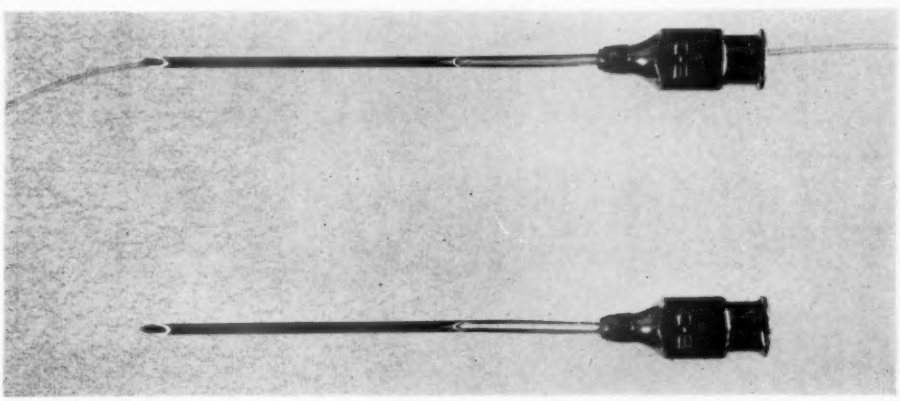


Fig. 1.—Slotted 18 gauge needle used for insertion of polyethylene tubing into an artery.

After the vessel has been closed, a segment of polyethylene tubing with an internal diameter of 0.011 cm. and an external diameter of 0.024 cm. is inserted into the proximal artery above the upper clamp. This tubing, which is quite flexible, can then be introduced through an 18 gauge needle devised by one of us (R. S. G.) and shown in Fig. 1. By means of a file, two sectors of the wall of the needle are removed over a space of 2 cm. The slot formed in this way facilitates the introduction of the polyethylene tubing into the artery. A purse-string suture of 00000 Deknatel braided silk should previously have been placed, and the needle inserted through the middle of this suture. As soon as the tubing is well within the lumen of the artery, which will become evident from the appearance of arterial blood in the polyethylene tubing, the needle is withdrawn, leaving the tubing within the artery. A 27 gauge needle is then inserted into the proximal end of the tubing and connected to a syringe containing the heparin solution, 20 mg. per cent in saline solution. The heparin solution should be injected into the artery as the purse-string stitch is tied down.

TABLE I

PATIENT, SEX, AGE, DATE	DIAGNOSIS	ARTERY INVOLVED	LENGTH OF OBSTR. (IN CM.)	DURATION ARTERIAL THROMBOSIS	ARTERIAL INCISIONS	METHOD OF INSERTION OF TUBING	LENGTH OF TIME IN PLACE	SYSTEMIC CLOTTING TIME (IN MINUTES)	FINAL CONDITION OF ARTERY	CLINICAL RESULT
(1) M, 66, 11/18/50	Trauma	Axillary & brachial	45	40 hr.	Resection & anastomosis, multiple transverse	Small branch below anastomosis	24 hr., Depo-heparin & Dicumarol	?	Patent	Gangrene tips thumb & 5th finger
(2) M, 48, 1/5/51	Buerger's trauma	Common & superficial femoral	2	3 hr.	Multiple transverse	Direct through stab wound with purse-string suture, com. femoral to iliac	6 days	4.5 to 25	Thrombosed	Improved
(3) F, 44, 1/31/51	Diabetes, atherosclerosis	Common & superficial femoral	1.5	8 mo. incomp.	Resection & anastomosis	Through 18 gauge needle with purse-string suture, com. femoral to iliac	5 days	12 to 21	Thrombosed	Improved
(4) M, 71, 1/19/51	Atherosclerosis	Common iliac	3	11 hr.	Multiple transverse	Through 18 gauge needle with purse-string suture, femoral to iliac	8 days	8 to 42	Thrombosed	Mid-thigh amputation
(5) F, 68, 2/6/51	Atherosclerosis	Femoral popliteal	10	2 mo.	Longitudinal	Percutaneous through 18 gauge needle into com. femoral	2 days, Dicumarol	17 to 21	Patent	Recovered

(6) M, 62, 2/8/51	Athero-sclerosis	Ext. iliac & com. femoral	15	2 wk.	Longitudinal	Through 18 gauge needle with fig. of 8 suture, com. iliac	2 days, Dicumarol	11 to 23	Patent	Recovered
(7) F, 3½, 2/10/51	Trauma	Axillary & brachial	15	30 hr.	Multiple transverse	Through 18 gauge needle into sub-clavian	6 hr.	?	Thrombosed	Died, aspiration pneumonia
(8) F, 41, 2/27/51	Diabetes, athero-sclerosis	Superficial femoral, popliteal	25	4 mo.	Longitudinal	Through 18 gauge needle, com. femoral	3 days, Dicumarol	23 to 29	Patent	Improved
(9) M, 73, 3/1/51	Buerger's disease, athero-sclerosis	Femoral popliteal	15	3 wk.	Longitudinal	Direct through needle	21 hr., heparin, Dicumarol	13 to 21	Thrombosed	Improved
(10) M, 71, 3/6/51	Athero-sclerosis, abdominal aneurysm, diabetes	Common iliac	10	2 yr.	Longitudinal, vein graft abd. aorta	Through needle into aorta above aneur.	4 days	23 to 126	Patent 4 days, then thrombosed	Died
(11) M, 52, 3/21/51	Athero-sclerosis, Buerger's disease, chem. trauma	Common iliac	10	Partial 3 yr.; complete 1 mo.	Longitudinal	Through 18 gauge needle with purse-string suture into aorta	5 days, Dicumarol	16 to 23	Patent	Recovered
(12) M, 58, 4/19/51	Athero-sclerosis	Femoral popliteal	15	4 mo.	Longitudinal	Through 18 gauge needle with purse-string suture, mid-femoral	8 days, Dicumarol 29 days	9 to 18	Patent	Recovered

Sufficient force should be used just to avoid occluding the polyethylene tubing. A free flow of heparin solution into the artery, and blood coming out when the injection pressure is released, are essential for the successful operation of regional heparinization.

When free flow has once been obtained, the polyethylene tubing is brought out to the surface of the body, not through the wound, but by means of passing it through an 18 gauge needle, three inches or more in length, inserted into the wound through some convenient place on the skin. The 27 gauge needle is then reinserted into the end of the tubing and the continuous injection of heparin solution maintained for the rest of the operation. It is advisable to leave one or more loops of polyethylene tubing close to the artery in order to furnish slack and permit the patient to move about freely in the postoperative period. It is also advisable to fasten the tubing to the skin close to its point of exit. Care should be taken so that the suture does not occlude the tubing. A free flow back and forth is essential at all times.

The clamps and rubber bands are then released from the distal artery and the branches. Considerable bleeding from the arteriotomy incision generally takes place but the pressure is low and the larger holes can be closed with figure-of eight stitches of 00000 Deknatel braided silk. It is important to point out that at this stage not too much time should be given to securing complete hemostasis, since the arterial blood which comes into the denuded vessel through the distal end and the branches is not under the influence of the anticoagulant therapy. A certain amount of thrombosis is desirable to prevent leaking along the suture line, but at the same time the development of a large thrombus inside the denuded vessel would vitiate the purpose of the operation. As soon as possible, therefore, the clamp on the proximal artery should be gradually released to provide for a rapid flow of blood through the previously occluded segment.

The hemorrhage from the line of closure may be alarmingly increased after release of the proximal clamp due to the high arterial pressure, but by judicious use of digital pressure along the suture line, possibly with the insertion of one or two more stitches, and with patience, satisfactory control of the bleeding can be accomplished. It may not be possible at first to discern pulsation in the artery distal to the suture line, possibly because of the thickened character of the wall or due to the diminished peripheral resistance. As long as heparinized blood is passing through the arterial segment and out through the branches, it is probable that the blood supply to the extremity has been improved.

The laying of Gelfoam soaked with fibrin along the suture line may afford additional protection, but it should be applied only after all significant bleeding has ceased.

Before closure of the operative wound, it is advisable to be sure that hemostasis is complete so that the restored artery cannot be compressed by the formation of a hematoma. We have not used drainage in any of our cases.

After the dressings have been applied and the patient returned to his bed, the polyethylene tubing, through which the heparin solution has been injected by an assistant since its original insertion, is secured to a tongue blade which

is strapped to the skin. There is a danger, in that, with angulation of the tubing, the hypodermic needle will pierce its wall. We have found it advisable simply to fasten the rubber tubing leading from the constant injection apparatus to the tongue blade, leaving a generous loop of polyethylene tubing loosely covered by a gauze pad between the tip of the needle and the point where it passes through the skin.

Various types of pressure injection apparatus are possible. We have used a constant injection pump, as illustrated in Fig. 2. Blakemore and Fitzpatrick[5] have recently described a pressure apparatus with a mercury escape valve. If a suitable pump is not available, it is possible to use gravity flow, provided that sufficient height above the patient's bed can be attained to permit a steady flow of solution at approximately 10 to 30 drops per minute.

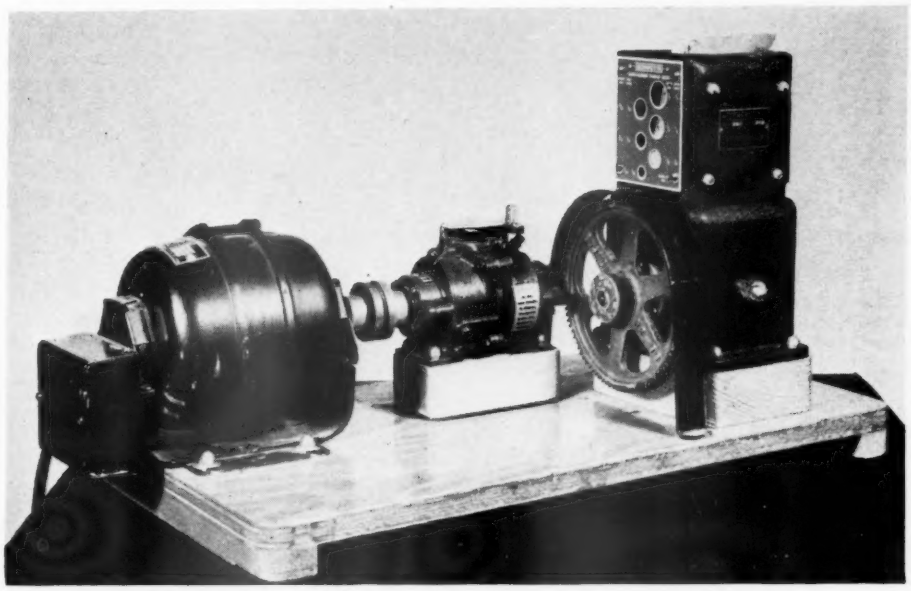


Fig. 2.—Injection pump used for the continuous intraarterial injection of heparin solution.

During the immediate postoperative period a constant intra-arterial injection of heparin solution, 10 mg. per cent in saline solution or 5 per cent glucose in distilled water, has generally proved satisfactory. The speed of injection has been altered in order to keep the systemic clotting time, as determined by the Lee-White method,[11] close to twenty minutes. This degree of systemic anticoagulant therapy is generally not hazardous. During the course of experimental work by one of us (R. S. G.), involving cross-transfusions,[12] it was demonstrated in patients that the clotting time of blood obtained as short a distance as two inches below the point of injection of the heparin solution has been prolonged from two to four times that of the systemic blood.

Attempts were made in several of the patients in this series to demonstrate that the clotting time of blood taken from the involved extremity was longer than the clotting time of systemic blood obtained at the same time. It has been

technically difficult to obtain blood from the involved extremity and in two patients, who had an inflammatory reaction of the distal tissues due to prolonged ischemia, the clotting time of the venous blood from the affected extremity was actually shorter than that of the systemic blood. We believe, therefore, that it is impractical to attempt to control the rate of intra-arterial injection of heparin solution by means of the clotting time of blood taken from the affected extremity. We have acted on the assumption that the clotting time regionally is greater than that of the systemic circulation.

Intra-arterial heparinization has been continued for from one to eight days, depending upon various technical factors. Ideally, it is our belief that it should be continued for at least two days and the patient then placed upon general anticoagulant therapy, since at the end of that time the danger of hemorrhage from the operative wound is minimal. We have generally stopped the intra-arterial heparin injection for at least six hours before removing the tube, to avoid the possibility of hemorrhage from the vessel at the site of insertion, but we have encountered no complications of this nature.

It is advisable to check the patency of the polyethylene tube at frequent intervals by discontinuing the injection temporarily to see if arterial blood comes back through the tubing. If the return flow is not free, it is possible that the tube may be blocked by a small clot. In such cases we have attached a 5 c.c. syringe containing heparin solution directly to the needle and by barbotage have restored the patency of the tubing.

Some of the complications which we have encountered have been attributable, we believe, to a dislodgment of the polyethylene tubing from the artery. The occurrence of this mishap can readily be demonstrated by the failure to obtain arterial blood when the pressure of injection is discontinued. In case it is impossible to obtain a free flow, it is advisable to remove the tube and to resort to systemic anticoagulant therapy.

Generalized anticoagulant therapy has been continued in this series of patients for a period of three to six weeks in order to permit endothelization of the arterial segments. Histologic material from clinical cases has not been available to determine the length of time necessary for this process to occur, but from the results obtained in clinical cases it appears that the danger of thrombosis is minimal after one to two weeks.

RESULTS

In Table I is given a brief summary of the results obtained in the first twelve cases. Two patients died, the first a 3-year-old child with bilateral Wilms' tumors who succumbed from aspiration pneumonia in the immediate postoperative period. At post-mortem examination the axillary and brachial arteries were found to be thrombosed, probably due to a technical failure of the constant injection pump. The second death occurred in a 71-year-old man, four days after operation, from acute myocardial failure. This patient also had an aneurysm of the abdominal aorta which was treated at the same operation by a vein-inlay graft.[13] The left femoral pulse had been restored to normal for four days after

operation, but at the end of that time it was noted that it was no longer possible to aspirate blood from the polyethylene tubing. Systemic anticoagulant therapy was immediately started, but post-mortem examination showed the arterial segment to be reoccluded. In Fig. 3 is shown the histologic appearance of the aorta at the site of insertion of the polyethylene tubing in this case.

Fig. 3.—Photomicrograph of wall of aorta at site of insertion of polyethylene tubing. A mild inflammatory reaction is apparent in the adventitia.

Recurrent thrombosis leading to the development of gangrene necessitated mid-thigh amputation in one patient, Case 4. This patient was a 71-year-old man, who developed an acute occlusion of the left iliac artery one week after partial cystectomy for carcinoma of the bladder. He was operated upon eleven hours after the onset of symptoms of acute arterial obstruction, with a preoperative diagnosis of arterial embolus. He proved to have a thrombosis of the common iliac artery at its bifurcation on the basis of atherosclerosis. The common femoral artery was first opened but no thrombus found, and accordingly the common iliac artery was exposed. An attempt was made to remove the occlusion through a transverse incision at the bifurcation of the common

iliac artery, and the polyethylene tube was then inserted into the common femoral artery and passed up into the common iliac artery above the second arteriotomy opening. Despite continuous intra-arterial injection of heparin over a period of eight days, the circulation never became restored. In retrospect, we believe that there were two errors in this case: (1) inadequate exposure, since the common iliac artery above the point of obstruction was not sufficiently accessible; and (2) passage of the polyethylene tubing up from below through the denuded vessel. In two other patients, Case 2 and Case 3, in which the polyethylene tubing was passed up from below, secondary thrombosis occurred. Fortunately, in both of these patients the clinical course was favorable and the extremities survived. A technical failure of the intra-arterial injection was responsible for an additional complication in Case 9. At the time of insertion of the polyethylene tubing into the midportion of the femoral artery, the vessel was so thickened and atheromatous that it was difficult to

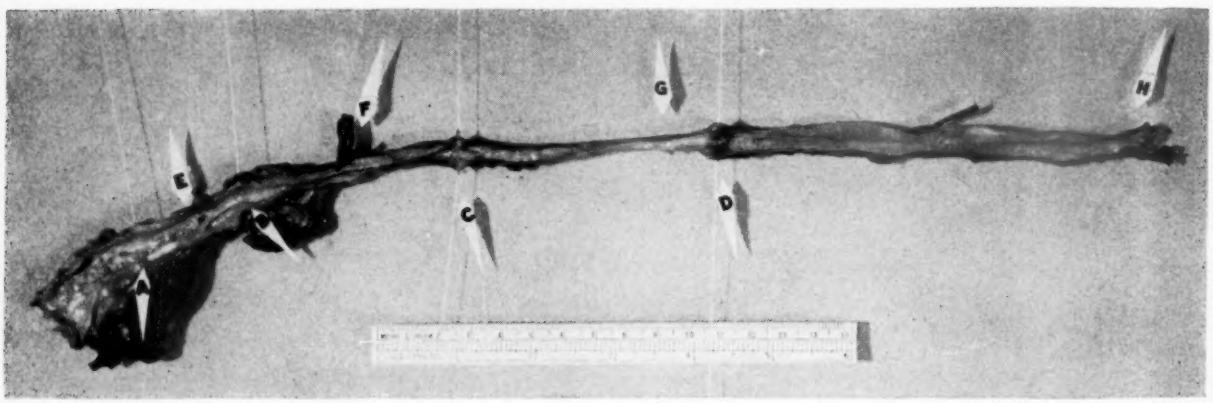
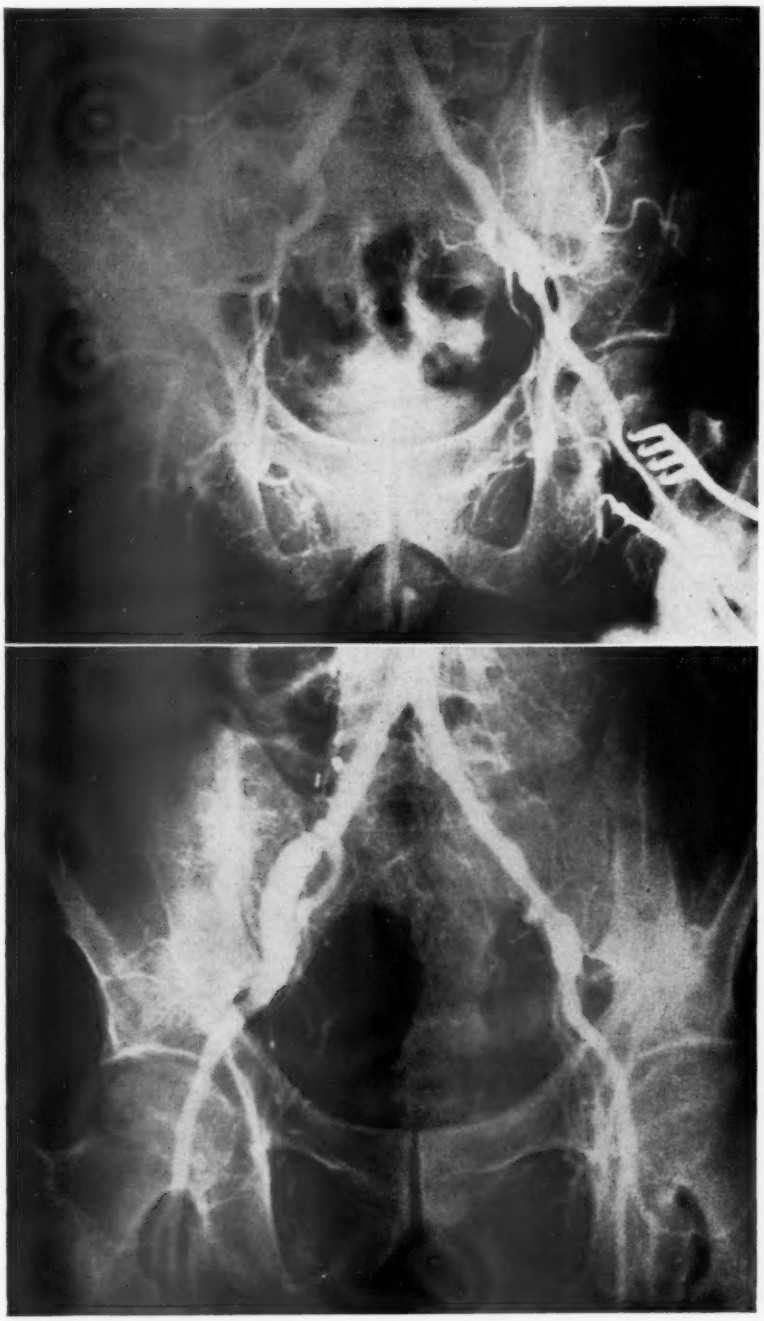


Fig. 4.—Left axillary and brachial arteries five months after extensive thrombectomy in Case 1. Letters *A*, *B*, and *C* indicate the sites of arteriotomy openings; *D* indicates site of end-to-end anastomosis.

make the insertion. A free backward flow of blood was never obtained. Despite this fact the injection of heparin solution was continued for twenty-one hours and the systemic clotting time adequately prolonged. The patient developed pain and induration over the course of the femoral vessels, however, so that the injection was discontinued and the patient placed on systemic anticoagulant therapy. Subsequently, he developed necrosis of the medial portion of the wound with a large subfascial hematoma. Ultimate healing took place, and although the patient was clinically improved, there was no evidence that the arterial segment had remained patent.

In six of the patients, restoration of the lumen of the obstructed artery was clearly demonstrable. In Fig. 4 is shown the specimen removed at postmortem examination five months following extensive thrombectomy in Case 1. This patient was operated upon forty hours after acute thrombosis of the axillary and brachial arteries had developed, following attempted passage of a catheter for the purpose of intra-arterial injection of nitrogen mustard in the treatment

A.



B.

Fig. 5.—*A*, Retrograde arteriogram demonstrating occlusion of right external iliac artery. *B*, Aortogram following thrombo-endarterectomy of right external iliac artery.

of metastatic carcinoma of the kidney. Adherent thrombi had been removed through multiple transverse incisions at the points indicated in Fig. 4, and in addition a segment of the thrombosed artery had been resected. The polyethylene tube was inserted through a branch of the brachial artery and regional heparinization continued for twenty-four hours, followed by general anticoagulant therapy. Despite the advanced ischemia in this case, with anesthesia extending to the upper forearm, there was complete restoration of the circulation with normal peripheral pulses, and the gangrene was limited to the tips of the thumb and fifth finger.

In Case 5, complete restoration of the circulation was demonstrable by the return of the ankle pulses and the disappearance of intermittent claudication.

Fig. 6.—Histologic appearance of organizing thrombus with part of the vessel wall removed in Case 6.

Fig. 5, *A* and *B*, shows the preoperative and postoperative arteriograms in Case 6. This patient was a 62-year-old man, who had developed signs of acute arterial occlusion of the right iliac artery two weeks before operation. There was marked ischemia of the foot, absence of pulses even in the right groin, constant rest pain, and impending gangrene of the distal part of the foot. In Fig. 6 is shown the thrombus with part of the vessel wall taken from the affected artery. In this case the incision in the arterial wall extended from the bifurcation of the common iliac artery to the origin of the superficial femoral artery.

Patency of the arterial segment was most likely in Case 8 because of the improvement in oscillometry and the healing of the lesion on the foot. This

patient was a 41-year-old woman with severe diabetes and a necrotic ulcer of the left great toe of four months' duration. At operation the occlusion was found to extend from the origin of the profunda femoris down into the popliteal space. In Fig. 7 is illustrated the "sequestrum" removed at the time of operation.

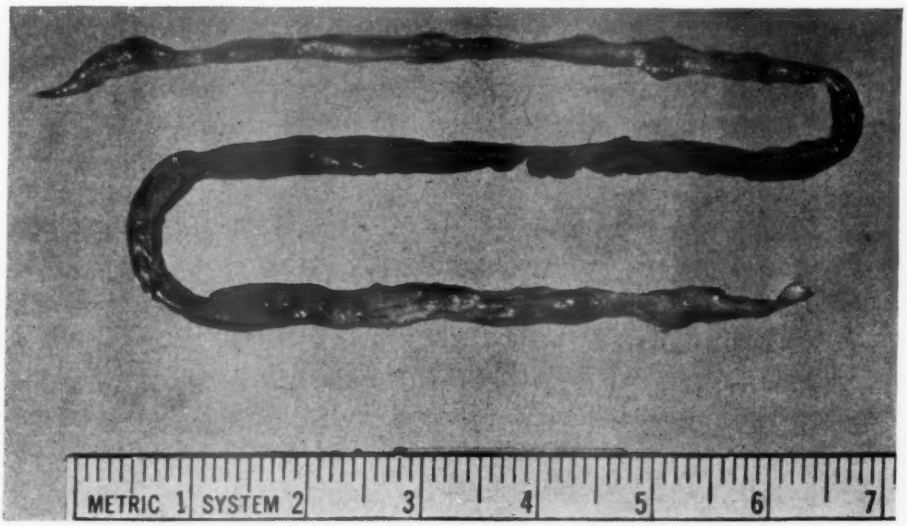


Fig. 7.—"Sequestrum" removed from femoral artery in Case 8.

A. *B.*

Fig. 8.—*A*, Preoperative aortogram and *B*, postoperative aortogram in Case 11 following thrombo-endarterectomy of left common iliac artery.

Fig. 8 shows the preoperative and postoperative arteriograms in Case 11. This 52-year-old man had evidence of incomplete obstruction of the left iliac artery of three years' duration. One month before operation an aortogram had been performed with the injection of 80 per cent sodium iodide. Although excellent visualization of the aorta and its branches was obtained, the patient

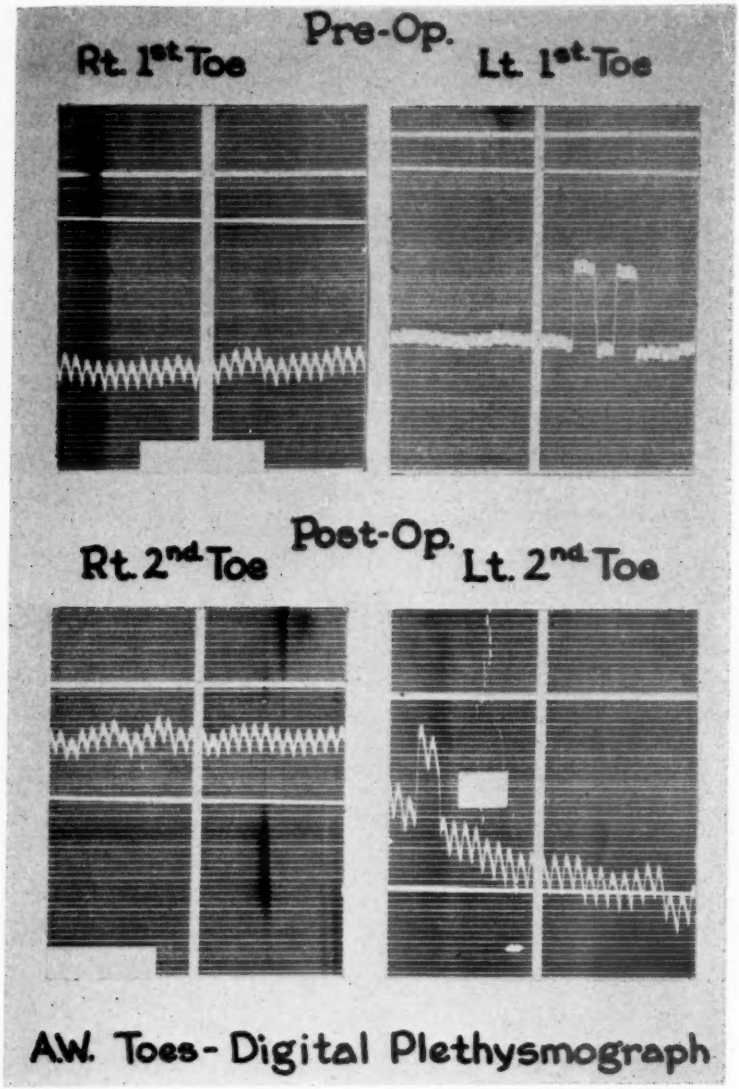


Fig. 9.—Digital plethysmography before and after thromboendarterectomy of left common iliac artery in Case 11.

developed signs of severe renal injury and after recovery from this complication, it was found at operation that the thrombosis had extended to involve the common iliac artery up to the bifurcation of the aorta. Complete restoration of the lumen of the artery was demonstrable both by the arteriogram and by the change in the digital plethysmography, shown in Fig. 9.

Case 12 was a 58-year-old man, who had developed signs of severe ischemia of the left leg four months previously. A left lumbar sympathectomy had produced some improvement, and at the time of this operation an arteriogram of the left leg, shown in Fig. 10, had demonstrated segmental obliteration of the femoropopliteal artery. Following thromboendarterectomy, the intra-arterial heparin was injected for eight days and the patient then placed on

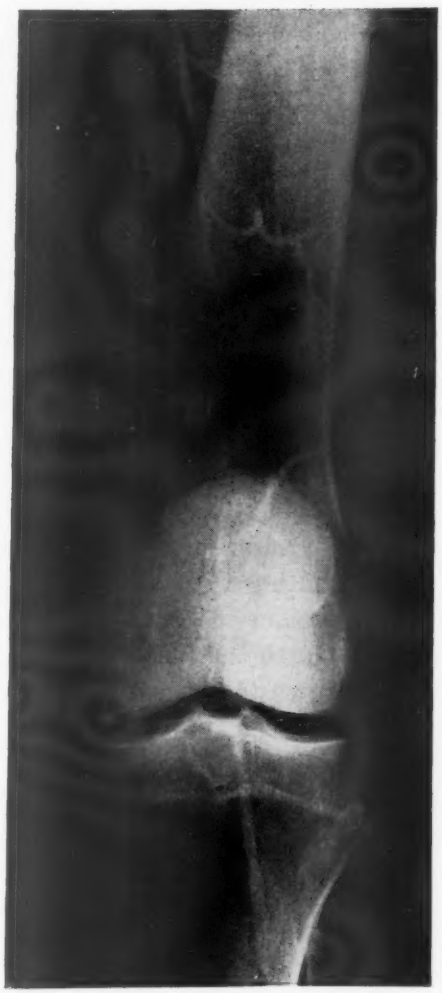


Fig. 10.—Preoperative arteriogram demonstrating segmental thrombosis of popliteal artery in Case 12.

Dicumarol. Two months later, pulses were readily palpable at the left ankle, the patient lost his rest pain, and the symptoms of ischemic neuritis had subsided.

DISCUSSION

The process of clotting is essential during and after operative procedures in order to prevent exsanguination and to permit wound healing. Operations on blood vessels pose a special problem since selective thrombosis is required.

It is essential not only to prevent bleeding from the wound but at the same time to prevent thrombosis within the artery which has just been repaired. Although it has been repeatedly demonstrated that operations are feasible, even with the patient under generalized anticoagulant therapy, postoperative bleeding is frequently a serious complication. It is logical, therefore, to keep blood from clotting in the vessel whose lumen has just been restored, and yet, at the same time, to allow the blood to clot elsewhere. The patency of the lumen in many of the patients following thromboendarterectomy, and the absence of hemorrhage as a complication in these patients indicates that regional heparinization is effective locally in preventing thrombosis, and at the same time does not cause undue bleeding from other vessels throughout the body.

Thromboendarterectomy may be of considerable benefit, at least temporarily, to patients with obliterative arterial disease. Its importance in the therapeutic armamentarium of peripheral vascular disease may be limited since although the obstruction is segmental there is generally widespread cardiovascular disease with extensive changes in other blood vessels as well. Even though the patency of the obstructed arterial segment may be restored by this procedure, the obliterative process may have extended distally to involve the smaller vessels so that functional recovery is not complete. Thromboendarterectomy can therefore not be considered a cure for vascular disease but simply as an adjunct in the general treatment of this condition.

It is possible that with restoration of the lumen after removal of part of the arterial wall, abnormal dilatation with ultimate aneurysm formation may develop. One of the contraindications to thromboendarterectomy mentioned by Arnulf is extensive calcification of the arterial wall with consequent weakening. The dilatation of the artery shown in the postoperative aortogram of Case 6 (Fig. 5) may produce complications in the future. The substitution of a new lining by use of a venous isograft may furnish protection against the development of aneurysmal dilatation. In another communication by one of us (N. E. F.) the use of a vein-inlay graft after thromboendarterectomy of the abdominal aorta has been described.[13] Only by the future course of patients who have been subjected to thromboendarterectomy can a proper evaluation of this procedure be made.

SUMMARY AND CONCLUSION

Regional heparinization for a period of one to eight days has been used in a series of twelve patients after thromboendarterectomy for obliterative arterial disease. Subsequent generalized anticoagulant therapy with Dicumarol was employed. Satisfactory restoration of the circulation resulted in six cases. Hemorrhage has not been a complicating factor in any of these patients. A detailed account of the techniques of regional heparinization and thromboendarterectomy is presented.

The authors are indebted to the Veterans Administration for permission to include Case 11 from the Fort Miley Veterans Hospital, and Case 12 from the Oakland Veterans Hospital.

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THE TRANSMETATARSAL AMPUTATION IN ARTERIAL DEFICIENCY OF THE LOWER EXTREMITY

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INTRODUCTION

THE patient who has obliteration of the peripheral arteries due to arteriosclerosis with or without diabetes, or to Buerger's disease, and who has an area of gangrene, an ulcer, or an infected sinus in the region of the toes or forefoot has always presented a problem in therapy. If one excludes such specialized and rare techniques as chemical amputation,[1] three courses have generally been considered available. These are (1) conservative therapy over a period of weeks or months in the hope that the lesion will heal spontaneously by casting off the necrotic part; (2) amputation of the lower extremity either through the lower leg or the thigh (hereinafter referred to as a "major amputation"); or (3) local amputation in the foot (hereinafter referred to as a "local amputation").

It is our experience that conservative treatment is practical only in patients whose cases combine the following features: (1) an economic independence which will enable the individual to live a crutch and wheelchair existence at home for the duration of healing; (2) such poor arterial circulation in the foot as to make the prognosis for the success of a local operation guarded; (3) the absence of pain; (4) a reaction of the surrounding tissues to the lesion which is favorable enough to make the likelihood of a flare-up of infection small. Such a combination of circumstances is rare. The conservative course is, therefore, seldom used except in patients who have an extreme degree of generalized arteriosclerosis or other degenerative disease which, irrespective of the situation in the foot, indicates a short life expectancy.

Amputation of the leg was, before the advent of penicillin, the operation performed on nine out of ten patients having surgery for gangrene due to obliterative arterial disease in diabetes mellitus.[2] It was then often done as a matter of urgent necessity. This was for two reasons. The first was that procrastination in a patient who entered the hospital with gangrene and cellulitis in the presence of poor circulation not infrequently led to further spread of infection and septicemia. The second reason was that prior to the antibiotics the hazards involved afforded less opportunity for development of techniques for amputations in the foot than has been possible since. Now it is the rare patient whose infection cannot be controlled either by drug alone or by drug

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plus local drainage in the foot, and the clarification of the principles of the transmetatarsal amputation by McKittrick[2, 3] allows for a reasonable optimism toward a local amputation when infection has passed.

First in 1946, and again in 1949, McKittrick and his associates reported experiences with a group of patients, eventually numbering 215, only 2 of whom died, and of whom 82 per cent were discharged from the hospital without major amputation. This stands as a significant contribution to the surgery of peripheral vascular diseases. A report by Furste and Herrmann,[4] in 1948, of results of a somewhat similar operation which they had performed in ninety-one selected cases, starting in 1934, showed a mortality between 8 and 14 per cent and satisfactory results in only 37 per cent. All their operations, however, were performed without primary closure, and many of them before the advent of penicillin.

Stimulated by the above reports, we have examined our own experience with the forty-three transmetatarsal amputations which have been performed for peripheral arterial deficiency in forty patients at the Massachusetts General Hospital in the five-year period, 1945 through 1949. Such a study seemed to have promise of practical value, since in contrast to the experience reported by McKittrick in which the operations were performed by no more than three or four different surgeons and nearly all the patients were suffering from diabetes mellitus, the forty-three operations at the Massachusetts General Hospital were performed by twenty-two different surgeons, on patients only 70 per cent of whom were diabetic. The comparison is, then, between a clinic with a small staff largely devoted to the special care of diabetes, and a general hospital with a large staff and major responsibilities in postgraduate surgical training. We thought that if the operation could stand the test implied by the latter conditions it could be considered practical for widespread use.

MATERIAL AND METHODS

Although during the five-year period under consideration fifty-one transmetatarsal amputations were performed on forty-eight patients, only the forty-three amputations performed on forty patients who had arterial deficiency are considered here. The eight amputations which we are excluding from consideration were done for osteomyelitis in the presence of good circulation and were thus virtually assured of healing (in seventy patients with good circulation McKittrick had only one failure). A study of the problem of securing healing in the foot with arterial deficiency must not be clouded by inclusion of patients with infection and good arterial circulation.

The amputation consists of division of the metatarsal bones at their narrowest portions just proximal to the head, through a skin incision designed to leave a long plantar flap (Fig. 1). The principles, which have been advocated by McKittrick, of careful and prolonged preoperative preparation with rest, antibiotics, and drainage of infection; meticulous atraumatic operative technique with primary closure and avoidance of tension on the wound edges; and avoidance of trauma to, or elevation of, the foot in the postoperative course were carried out in these patients.

The group has been analyzed in regard to successful salvage of limbs, economic factors at stake, and later rehabilitation.

Limb Salvage.—Table I shows that in 62.8 per cent of the cases the operation was successful in that the limb was not lost. In eleven (42 per cent) of the extremities which were not lost, however, there was a delay in healing. Most of these eleven were discharged with a small open area (Fig. 2) which later healed on ambulatory therapy.

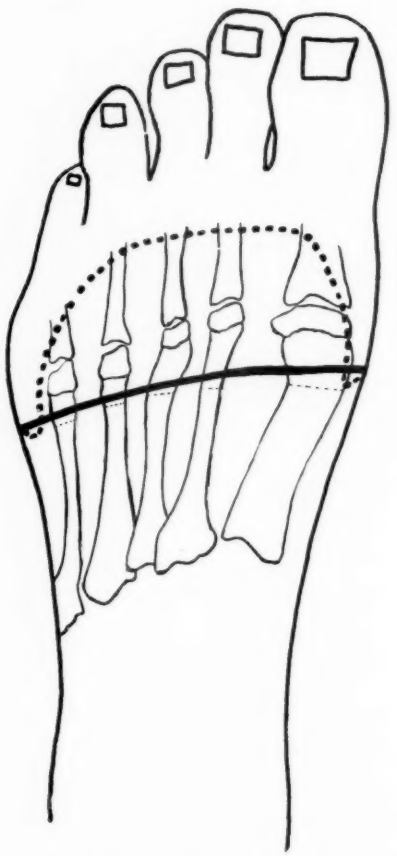


Fig. 1.—Diagram showing lines of incision for transmetatarsal amputation.

How many of these salvaged limbs would have survived prolonged conservative therapy, or indeed how many of those which were lost following operation would have been lost after conservative therapy also, cannot be determined. The estimate of McKittrick[2] that 10 to 15 per cent of limbs are saved by the procedure seems to us extremely low. All the patients subjected to transmetatarsal amputation had ischemic lesions involving the deeper structures (tendon, joint capsule, bone, or periosteum) of toe or foot which could have healed only by the separation of these tissues. Although three of the unsuccessful amputations we feel might have healed had there not been an error in judgment or technique or a misadventure such as misunderstanding or lack of cooperation on the part of the patient, there was in none of the patients any practical alternative to some sort of amputation.

TABLE I. FORTY-THREE TRANSMETATARSAL AMPUTATIONS,* MASSACHUSETTS GENERAL HOSPITAL, 1945 THROUGH 1949

DIAGNOSIS	HEALED PER PRIMAM	DELAYED HEALING	STILL UNHEALED	FAILED	OPERATIVE MORTALITY
Arteriosclerosis					
Diabetic	11	8		11	0
Nondiabetic	4	2	1	4	0
Thromboangiitis obliterans	0	1		1	0
	15(34.9%)	11 (25.6%)	1(2.3%)	16 (37.2%)	
Total Successes		27(62.8%)			

*All extremities had impaired arterial circulation.

Table II furthermore demonstrates that in the five-year period under consideration there was a greater decrease in the incidence of major amputations performed, as compared with that of local amputations. Although study of the individual records of all these patients has not been made, the trend toward limb salvage seems hopeful.

TABLE II. DECREASE IN LOWER EXTREMITY AMPUTATIONS, 1940 THROUGH 1949

	1940-1944	1945-1949	DECREASE (PER CENT)
Major amputations	275	203	26.1
Local amputations	214	183	13.4

SOCIOECONOMIC CONSIDERATIONS

The average age of the patients was 65.1 years with extremes of 37 to 87 years. (If one excludes the two patients with Buerger's disease the youngest age was 48 years.) This was slightly higher than the mean of 61.5 years which prevailed in McKittrick's series.

TABLE III. THIRTY-NINE* PATIENTS WITH TRANSMETATARSAL AMPUTATION; NUMBER OF HOSPITAL DAYS AFTER OPERATION, MASSACHUSETTS GENERAL HOSPITAL, 1945 THROUGH 1949

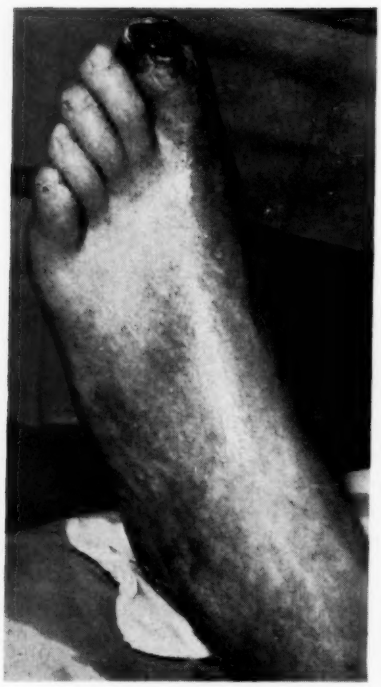
	HEALED PER PRIMAM	DELAYED HEALING	FAILED	TOTAL
Number of patients	14	11	14	39
Mean postoperative hospital days	21.2	36.5	47.8	35.1

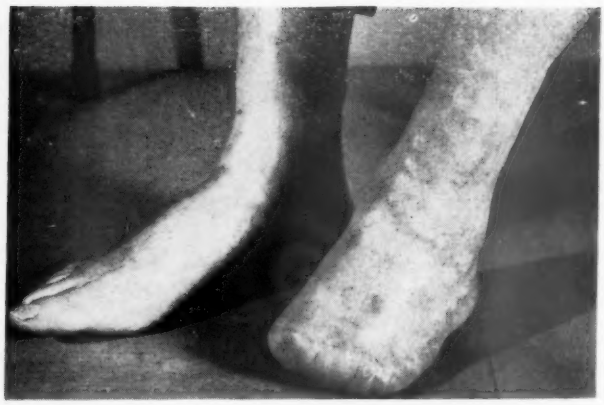
*Because of complicating diseases in one patient the postoperative hospital days as they pertain to the transmetatarsal amputation could not be analyzed.

Most patients with degenerative arterial disease are retired from work, and a prolonged hospitalization seems less easily financed and perhaps not so purposeful as earlier in life. Table III demonstrates the mean numbers of days our patients spent in the hospital following amputation. It can be seen that the figure for the total group was five weeks. This varied from three weeks for those healing per primam to five and seven weeks respectively for those healing in a delayed manner and those failing to heal. The figure of five weeks is perhaps misleading since no account is made of the length of time in the hospital devoted to preparing the extremity for operation, a period usually of seven to fourteen

days. It is of interest, however, that of the forty patients, an average total time of 86.9 days was devoted to the hospital care of their extremities for obliterative arterial disease. The episode surrounding the transmetatarsal amputation covers, then, about half the hospital time required by these patients for the care of their extremities, up to the date of analysis.

B.





A. *C.*

Fig. 2.—Case McP., 82 years old. *A*, Photograph of necrotic area on the tip of the left great toe. There was an additional necrotic lesion, which is not visible, on the medial surface of the left fifth toe. *B*, Stump eighteen days after operation. Note small area of necrosis in lateral aspect of the incision. *C*, Appearance of healed stump two months after operation. The patient was ambulatory and active.

The issues raised by these considerations are largely philosophical ones and are beyond our power to resolve. Our mission is to rehabilitate the patient as a whole by saving his leg, while at the same time being careful to avoid demoralizing and bankrupting attempts to heal an ulcer or an operative wound in a hopelessly ischemic foot. To this end it is hoped that more intimate knowledge of the prognosis of the individual extremity will help us decide earlier for higher amputation in cases similar to those which have failed.

Late Results.—In twenty-seven patients the amputation was successful. Table IV demonstrates their subsequent fate as recorded at the time of follow-up examination. Nineteen (70.3 per cent of the extremities excluding the single patient with a small persistent draining sinus) have remained healed and useful until now. Five (18.5 per cent) others remained healed and useful until death which was due to unrelated causes (one to carcinoma of the pancreas, two to cerebrovascular accidents, two undetermined). One (3.7 per cent), due to a careless injury, later lost the limb on the side of the transmetatarsal amputation, the foot having been useful until that time. Two (7.4 per cent) of the patients were lost to follow-up.

TABLE IV. LATE RESULTS IN TWENTY-SEVEN PATIENTS HAVING SUCCESSFUL TRANSMETATARSAL AMPUTATIONS, MASSACHUSETTS GENERAL HOSPITAL, 1945 THROUGH 1949

	NUMBER	PER CENT	MEAN LENGTH OF FOLLOW-UP MONTHS
Good result until now	19	70.3	37
Good result temporarily, died later	5	18.5	8*
Good result temporarily, lost limb later	1	3.7	29*
Lost to follow-up	2	7.4	

*Time until death or loss of limb, whichever applies.

There are additional data of interest. In this group of successful cases, three patients have lost the contralateral limb and all but three were or are able to be as active as before the onset of the lesion for which the operation was done. The latter three were less active due to calluses on the stump. Of the eleven patients who were discharged with an open area still present which later healed, the time necessary for healing averaged 4.3 months (extremes of 1½ to 12 months).

It is obvious that from an orthopedic standpoint, the foot is not as efficient as one in which the transverse arch is preserved, but whereas in an active youth the operation would be handicapping, in this group of patients a full degree of activity for their age and infirmity is possible. Most of them need no special shoe, and no prosthesis other than a wad of paper or cotton inserted in the toe of the shoe.

DISCUSSION

Factor of Diagnosis.—Although in Table I the individual diagnosis groups, when subdivided, are small, there is no detectable tendency for any one of them to show a more favorable prognosis for healing the operative wound than another. The per cent of success among thirty arteriosclerotic patients with diabetes was, for example, 63.3 per cent, that among eleven arteriosclerotic patients without diabetes was 63.6 per cent, and that among two patients with Buerger's disease was 50 per cent.

Factor of Age.—The oldest three patients were in their ninth decade at the time of amputation, 81, 82, and 87 years of age, respectively. The amputation

healed in the individuals of 81 and 87 years, failed in the 82-year-old patient. It is apparent that advanced age alone is not an important factor in determining prognosis.

Factor of Sex.—In twenty-nine of the cases of amputation the patients were men, in fourteen, women. The incidence of successful healing in the twenty-nine men was seventeen (58.7 per cent), in the fourteen women, ten (71.5 per cent). This apparent tendency toward a poorer prognosis in men, if borne out in a larger series of cases, would conform to the well-known fact that sclerosis of arteries is more marked in men than in women.

Degree of Arterial Deficiency.—The extremities were divided into two groups, according to the degree of circulatory impairment, namely, moderate, of which there were thirty-three instances, and marked, of which there were ten. Criteria for placing the extremity in the category of impaired circulation were absence of pedal pulses and any degree of ischemic rubor on dependency. Of this group, those with no pulses below the common femoral artery, an extreme degree of ischemic rubor on dependency, rest pain, and extremely poor bleeding at the time of operation were considered to have marked arterial deficiency. The remainder were classified as moderate. In eight (80 per cent), of the ten extremities with marked deficiency, healing failed to occur, the figure for the thirty-three extremities with moderately impaired circulation being eight (or 24.2 per cent).

The degree of arterial deficiency is obviously the one most important criterion for determining prognosis. In its evaluation, well-tried clinical methods have served better than laboratory tests. We are not prepared, however, to state that the prognosis is hopeless even if the three cardinal signs of advanced arterial impairment (no pulses below the femoral artery, maximal ischemic rubor on dependency, and rest pain which does not respond to therapy) are present. We have had occasional successes in the face of each of these conditions.

Other Lesions.—The presence of another lesion on the heel or the external malleolus is occasionally noted and thought by some to be a contraindication to transmetatarsal amputation for a lesion of the toes or forefoot. One such instance occurred in this series and did not interfere with healing of the amputation or later ambulation. Whether to perform transmetatarsal amputation under such circumstances depends primarily on the ability of the tissues of the foot or ankle to react favorably to the lesion during the period of preoperative preparation.

Care of Postoperative Ulcers.—In treating the eleven patients who were discharged from the hospital with their incisions unhealed and who healed them later, and the patient who has had a persistent sinus for two years, it is important that such areas are easier to dress and safer to treat conservatively than similar lesions of toes in the intact foot. Maceration of tissue and inadequate drainage of sepsis both can be better dealt with in the more open field of the transmetatarsal stump. Furthermore, there is less local motion to dislodge dressings or to stir up infection. In the immediate proximity of the incision there are no joint capsules, cartilages, or tendons, structures which are poorly resistant to infection.

Lumbar Sympathectomy.—Prior lumbar sympathectomy was performed in four extremities, in three of which the transmetatarsal amputation healed successfully, and in one of which it did not. Two of these patients were in the younger diabetic group and two had Buerger's disease. The failure was one of the latter. This experience has been so limited that on the basis of it alone we cannot discuss the value of preliminary sympathectomy. In another series of seventeen amputations performed by one of us, prior lumbar sympathectomy had been performed in eight cases, with an incidence of successful healing of the amputation in 64 per cent. On the basis of this experience, we do not believe that prior lumbar sympathectomy, though perhaps useful in certain instances, should be recommended as a routine for all patients receiving local amputations.

Other Types of Local Amputation.—Table II emphasizes that the transmetatarsal amputation is not the only local amputation performed in our clinic. Amputations of the first and fifth toes through the narrow subcapital portions of their metatarsals, or of the second, third, and fourth toes through the proximal phalanges are not infrequently performed for ischemic necrosis distal to the mandatory lines of incision for these operations. The same principles of preparation, technique, and after care apply here as for the more proximal transmetatarsal amputation. The latter has the value of being applicable to lesions in a wider variety of locations, particularly those at the base of the toes, and of having a more favorable prognosis for healing in patients in whom the circulation to the toes is strikingly inferior to that a few centimeters more proximal in the foot. In the case of a lesion located so as to be amenable to either operation in a foot which is uniformly ischemic in both toes and forefoot, the transmetatarsal amputation has the disadvantage of being more susceptible to tension on the wound edges than the amputations of single toes. These factors are considered in each case.

Evaluation of Results.—In the group reported by McKittrick and coworkers, the incidence of eventual healing of the operative wound in patients with impaired circulation was about 75 per cent. Our incidence of 62.8 per cent is a reflection of a more limited experience and a wider variation of techniques. It is of interest, however, that in the last fifteen months' period of the study the incidence of successes rose from 50 per cent to 71.4 per cent, due to more careful supervision and standardization of the techniques. We believe that the operation has earned for itself a reputable position in the armamentarium of any surgical clinic.

SUMMARY

1. The transmetatarsal amputation has been used forty-three times in patients with peripheral arterial deficiency at the Massachusetts General Hospital in a five-year period.

2. In 62.8 per cent of the patients the wounds healed and the patients had useful limbs.

3. During the span of the period under consideration the total number of amputations performed for arterial deficiency decreased by 21 per cent in

comparison to the preceding five-year period. The number of major amputations decreased to a greater extent (26.1 per cent) than that of the minor (13.4 per cent).

4. The average postoperative stay in the hospital was five weeks.

5. In 11.1 per cent of the successful cases the foot was slightly less useful after amputation than it had been before it had developed the ischemic lesion. In the remainder (88.9 per cent) it was at least as useful as before.

6. The chief factor influencing unfavorable results was the degree of circulatory impairment, which was best determined by conventional clinical methods.

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THE GROWTH OF PRESERVED AORTA HOMOGRAFTS

An Experimental Study

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IN PREVIOUS experiments on pigs we found that there was no limitation of growth of fresh aorta autografts and that the grafts had the appearance of normal aorta, both grossly and microscopically.[1] There was also no limitation of growth of fresh aorta homografts, unless thrombosis occurred, but degenerative changes were noted in the graft walls. Thrombosis was a much more frequent complication of fresh homografts than of fresh autografts.

In the present experiments aorta homografts were implanted in young pigs after preservation in a nutrient solution for varying periods of time. The object was to study the growth of aorta homografts after preparation by methods currently used in artery banks.[2]

EXPERIMENTAL METHODS

A pig which weighed 25 pounds was sacrificed and its aorta was removed under aseptic conditions. The aortic branches were tied with fine silk ligatures. The aorta was divided into segments 2.5 cm. in length. These were placed in the preservative solution recommended by Gross and associates,[3] and refrigerated at 4° C. Nine grafts were prepared in this manner and they were implanted after the following periods of preservation: two after five days, two after seven days, one after nine days, three after fourteen days, and one after twenty-eight days.

The aorta of the recipient pigs was exposed retroperitoneally through a left flank incision. The lumbar arteries were ligated and divided, aortic clamps were applied, and a 2 cm. segment of the aorta was excised. The graft was sutured into place with simple interrupted sutures of 00000 Deknatel silk in order to avoid limitation of growth due to the method of suture.[4] On the day after operation the pigs were taken to the University Farm, where they were raised. When sacrificed about six months later their weight had increased to from 225 to 250 pounds, an eight- to tenfold increase. The increase in the cross-sectional area of the aorta was proportional to the increase in weight. Portions of the abdominal aorta which included the grafts were removed. Measurements and photographs were taken with the grafts and adjacent abdominal aorta inflated with saline solution to a pressure of 120 mm. Hg. Additional measurements and photographs were taken with the specimens opened longitudinally, and all the specimens were examined microscopically.

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RESULTS

The results of the experiments are summarized in Table I. Normal growth, such as that of fresh autografts and some fresh homografts, did not occur in any instance. All of the grafts except one were constricted to some extent. A representative specimen is shown in Fig. 1. The constriction was more apparent when the specimen was inflated than when it was opened because the graft was inelastic, whereas the aorta above and below was normally elastic. One graft was dilated (Fig. 2).

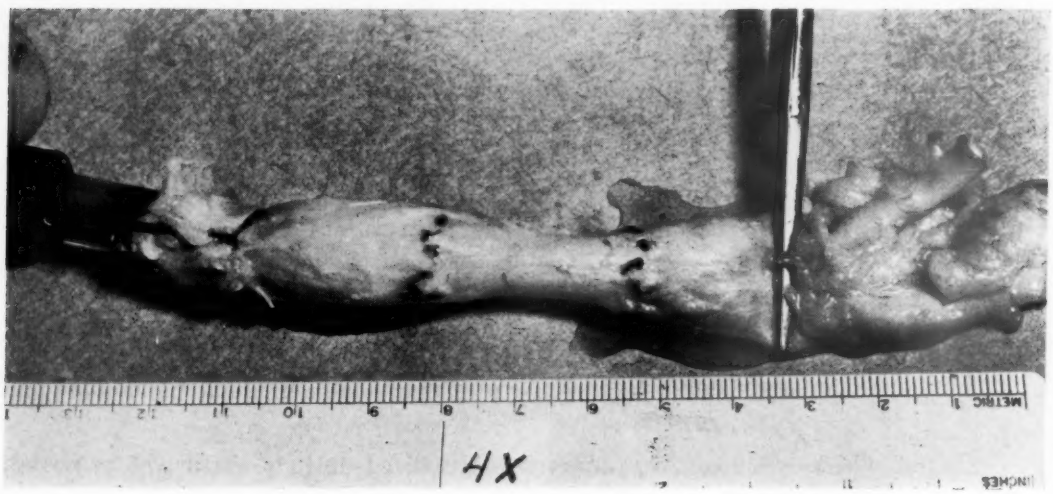

Fig. 1.—An inflated graft, which had been preserved for fourteen days (pig 4x). The constriction is apparent.

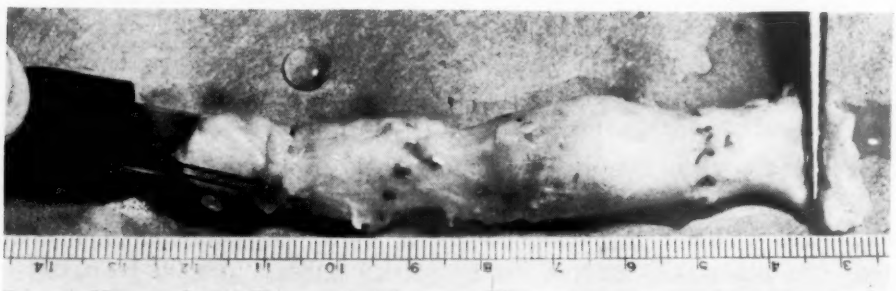

Fig. 2.—An inflated graft which had been preserved for five days (pig 7). There is partial constriction and partial dilatation.

Grossly, the intimal surface of the grafts appeared irregular and wrinkled. This is illustrated in Fig. 3. The grafts felt stiff and thick, in contrast to the softness and pliability of the recipient aortas. In two grafts a large amount of calcium was visible grossly. Fig. 4 shows a large calcium plaque in a specimen preserved for seven days. Fig. 5 shows a solid band of calcified media which completely surrounded a graft preserved for twenty-eight days.

Microscopically, severe changes were seen in all of the grafts. There was considerable thickening of the intima, while the media was greatly thinned.

Other characteristic changes in the media were inflammation, condensation and disruption of elastic fibers, and necrosis. When much calcification was present the media appeared to be completely necrotic and the elastic fibers were fragmented. Fig. 6 is a representative section.

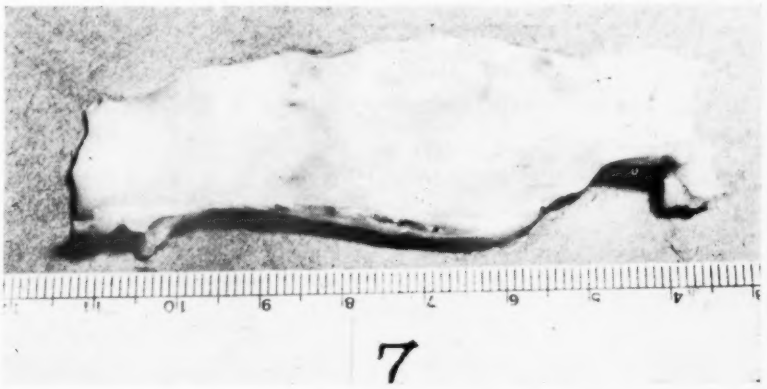

Fig. 3.—Specimen shown in Fig. 2 opened longitudinally. The irregularity and wrinkling of the intimal surface are clearly seen.

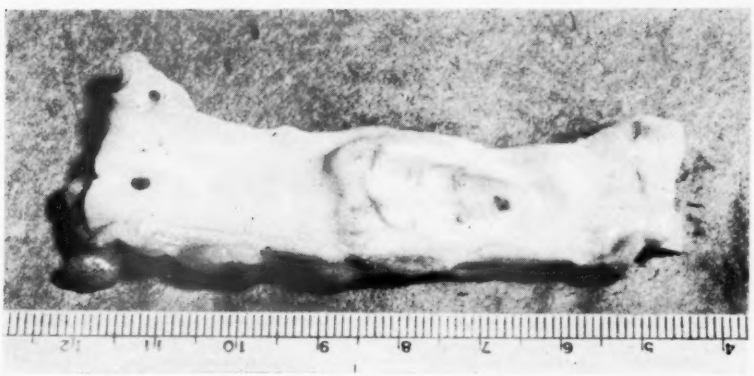

Fig. 4.—A graft preserved for seven days (pig 9). Specimen opened longitudinally. A large calcium plaque has replaced most of the media.

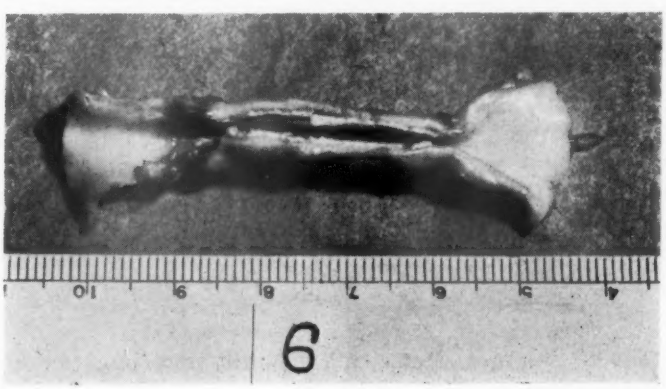

Fig. 5.—A graft preserved for twenty-eight days (pig 6). Specimen opened longitudinally. The media is replaced by a band of calcium.

COMMENT

In previous experiments with fresh homografts, degenerative changes were noted in the graft walls.[1] These were considered to be due to tissue incompatibility, since such changes did not occur in fresh autografts. Similar, but considerably more severe, changes occurred in these preserved homografts. It is evident, therefore, that "preservation" was not completely successful, in that the degenerative changes were more severe than in the fresh homografts. No definite correlation between the severity of the degenerative changes and the length of preservation could be demonstrated in this small series.

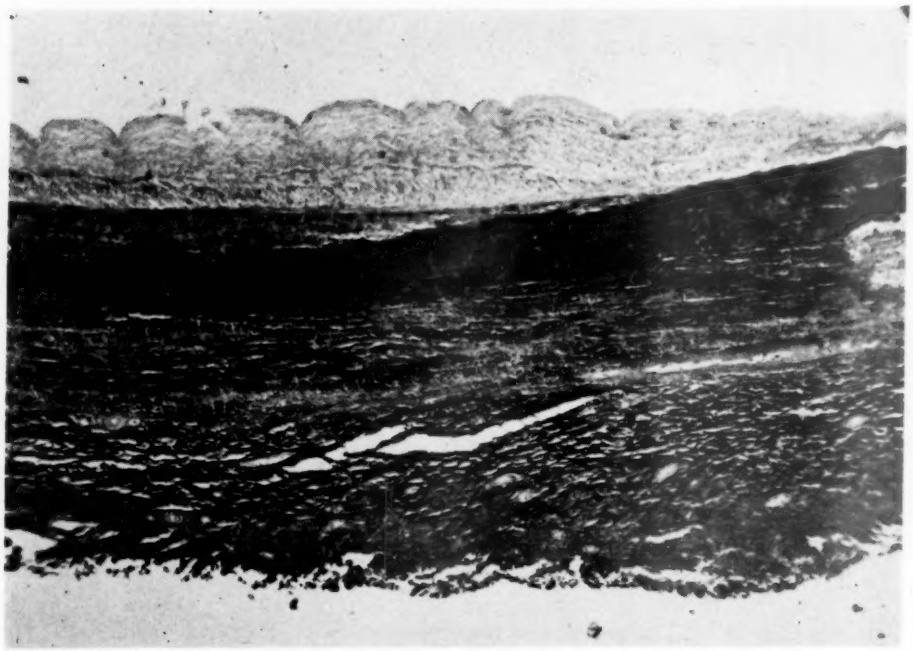

Fig. 6.—Low-power photomicrograph of graft in pig 9, preserved 7 days before grafting. The media is almost completely necrotic and calcified. Some intimal thickening and adventitial scarring are also evident.

CONCLUSIONS

1. Aorta homografts preserved in a nutrient solution for periods varying from five to twenty-eight days were implanted in young pigs and the fate of the grafts was studied after the pigs had attained full growth.

2. There was limitation of growth of all of the grafts except one, which was dilated.

3. Degenerative changes, consisting of inflammation, necrosis, or calcification occurred in all of the grafts.

TABLE I. SUMMARY OF EXPERIMENTS

ANIMAL NUMBER	DAYS GRAFT PRESERVED	HOST AORTA DIAMETER (IN MM.)		GRAFT DIAMETER* (IN MM.)		GROSS APPEARANCE OF GRAFT†
		OP.	SAC.	OP.	SAC.	
1	5	5				Thrombosed; thin, solid cord
7	5	6	14	5	18	Dilated; greatly thickened
9	7	6	15	8	9	Constricted throughout; large calcium plaque in media
2x	7	6	14	7	9	Partially constricted, especially at one point
2	9	7				Thrombosed; thin, solid cord
4x	14	8	14	8	6	Constricted throughout
5	14	7	13	6	6	Partial constriction
4	14	7	14	8	9	Partial constriction, marked at one point
6	28	6	12	8	8	Constricted throughout; solid band of calcium replacing media

*In the sacrificed pigs, when the grafts were not uniform in diameter, the measurements were taken at the point of greatest constriction, except in pig 7, in which the point of greatest dilatation was measured.

†All of the grafts increased slightly in length.

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EXPERIMENTAL CARDIAC SURGERY

III. Coronary Blood Flow as Measured Directly With the Caval Venous Return Shunted Past the Right Heart

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UP TO the present time, investigators[1-4] who have developed and employed mechanical heart-lung systems in experimental animals have concerned themselves primarily with the removal of the systemic venous blood. However, ultimate success in the performance of surgery on the open heart will depend upon a technique which will make it possible to remove all of the venous return to the heart. This will include the venous return from the body to the right auricle through the venae cavae, the venous return from the heart muscle mainly to the right auricle and ventricle through the coronary and thebesian veins, and finally, a portion of the bronchial venous return to the left auricle through the pulmonary veins.[5]

One might assume that with the systemic venous return excluded from the heart, the coronary venous return would offer no major obstacle to the performance of surgery on the open heart, since it would be possible to remove a relatively small volume of blood with a sump. However, under certain circumstances, the coronary venous return may be so large that its removal would be extremely difficult. It is important, therefore, that a detailed study of the coronary venous return be made under conditions simulating those which might be encountered during operations on the open heart.

The purpose of this paper is to report a series of studies on the volume of the coronary venous return to the right side of the heart with the systemic venous return shunted past the right heart into the pulmonary artery.

The coronary circulation has been investigated extensively in dogs and more recently, by indirect methods, in man. The contributions of Starling,[6] Anrep,[7] Gregg,[8, 9] Eckenhoff,[10, 11] Bing,[12] and their co-workers have been outstanding. The earliest measurements of coronary flow were made by perfusing blood through one or more of the branches of the right and left coronary arteries in isolated hearts or in heart-lung preparations. Anrep[7] found that 50 per cent of the coronary flow in dogs enters the circumflex branch of the left coronary artery, that 30 per cent enters the anterior descending branch of that artery, and that 20 per cent enters the right coronary artery. Thus, by calculation, a rough figure for total coronary flow can be estimated from these earlier works

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in which single coronary arterial branches were perfused. Most of these studies were performed under highly abnormal conditions, and the validity of the figures is questionable.

On the venous side, Evans and Starling[13] studied the distribution of the coronary venous return in dogs using a Morawitz cannula to collect the blood from the coronary sinus. They found that about 60 per cent of the total coronary flow entered the right auricle through that channel. Anrep[7] and Gregg[9] arrived at slightly higher figures for the coronary sinus return. However, Lendrum, Kondo, and Katz,[14] using a clever, though not entirely foolproof, technique to measure the partitioning of the coronary venous return in dogs' hearts immediately after death, found that an average of only 36.4 per cent of the coronary return flowed through the coronary sinus; 24.5 per cent of the blood entered the right auricle directly through the cardiac veins, and 30.8 per cent drained into the right ventricle. Interestingly enough, an average of 7 per cent of the return was found to drain into the left ventricular cavity. Therefore, in measuring the coronary sinus flow, either with a Morawitz cannula or by the nitrous-oxide method,[11] the values obtained for total coronary flow depend on the figure that is assumed to be correct for the percentage of coronary blood draining through the coronary sinus. Coronary sinus flow can also be expressed in terms of "cubic centimeters of blood per minute per 100 grams of heart with venous drainage into the coronary sinus."[8]

Since all the values for normal total coronary flow reported in the literature have been derived indirectly, by calculation, the reported figures for changes in coronary flow under a variety of experimental conditions cannot be quantitatively accurate. Even if they were accurate, they might not apply directly to experiments where the influence of extravascular compression is considerably decreased by the exclusion of the systemic venous return from the right side of the heart.

METHOD

The pump described by Sewell and Glenn[15] was used to shunt the venous return to the right side of the heart directly into the pulmonary artery. The pump has been described in detail by these workers. A slightly modified pumping chamber*[16] (Fig. 1) has been used in these experiments. As in the original model, total blood flow through the pump is measured continuously, without interrupting the flow, by means of a venturi in the outlet tubing attached to a flow meter.

Although the pump has a variable rate up to 150 cycles per minute, for the sake of uniformity all experiments were performed with a constant rate of 120 cycles per minute, at which rate the maximal output through the several arterial cannulae was somewhat over 2,500 c.c. of blood per minute. This maximal output was more than adequate to accommodate the total venous return obtained in all of the dogs studied in this series.

Prior to the performance of the experiments described in this report the flow meter was calibrated with whole blood. If the vacuum-pressure relation-

*We would like to express our appreciation to James Mullin, II, of Experiment Incorporated, Richmond, Va., who provided us with the pump and power unit.

ship in the pump remains constant and not excessive for the blood available for pumping, nearly repeatable values can be obtained for all but the highest flows (above 2,000 c.c. per minute) and the lowest flows (below 500 c.c. per minute), using the same arterial and venous cannulae and the same rubber tubing in the pumping chamber. We do not mean to imply, in recording total flow readings to the cubic centimeter of blood per minute, that we believe these values are of that degree of accuracy. However, the error for any recorded value for total flow in the living animal is probably not greater than ±20 c.c. per minute.

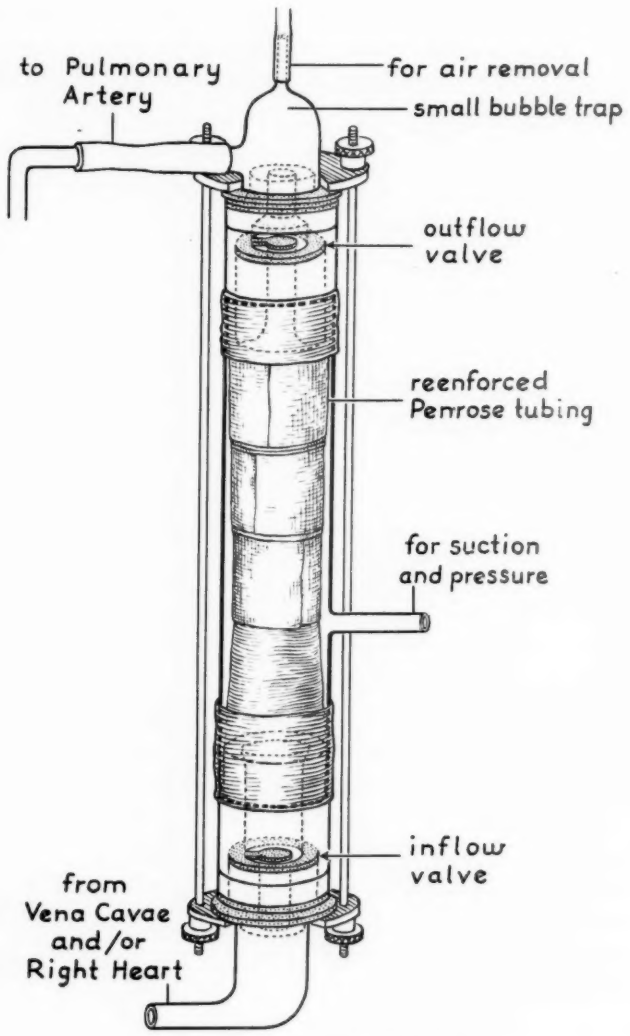

Fig. 1.—The pumping chamber.

Total coronary blood flow was measured directly in dogs of nine to twenty-two kilograms of body weight. The dogs were anesthetized with Nembutal, 30 mg. per kilogram. All operative procedures were carried out as rapidly as possible and under nonsterile conditions. The right femoral artery was cannulated for direct blood pressure measurement with a mercury manometer, and

a slow infusion of 5 per cent glucose in water was started in the femoral vein. A 6 cm. segment of external jugular vein on the right side was isolated, the dissection being carried down to the beginning of the right innominate vein. The exposed segment of vein was covered by a saline-moistened sponge and left to be cannulated after completion of the thoracic part of the procedure. An endotracheal catheter was inserted and connected to a positive pressure (Rand-Wolfe) respirator which was begun at the moment the right pleural cavity was opened. The lungs were insufflated twenty-two to twenty-five times a minute with 100 per cent oxygen. The right pleural cavity was opened through the fourth intercostal space or through the bed of the fifth rib. The azygos vein was ligated and divided, and the right pulmonary artery was carefully dissected almost to its origin at the main pulmonary artery. Ligatures of heavy silk were loosely placed around the superior and inferior venae cavae. The pericardial cavity was entered and a ligature loosely placed around the base of the main pulmonary artery without displacing the heart. Finally, a purse-string suture was placed, but not tightened, around the base of the right auricular appendage. This completed the preliminary dissections. At this point 5 mg. of heparin per kilogram of body weight were given intravenously. The main branches of the right pulmonary artery were ligated, and a glass cannula with an internal diameter of 8 mm. then inserted into the right pulmonary artery and tied in place with its lumen directed toward the left pulmonary artery. Next, the venous cannula, a segment of polyethylene tubing 36 cm. in length with an internal diameter of 6 mm., was introduced through an incision made in the peviously exposed right external jugular vein, passed into the superior vena cava, through the right auricle, and into the inferior vena cava. As illustrated in Fig. 2, this tubing has holes at its distal end for admitting the inferior caval blood, another series of holes 8 to 10 cm. above for admitting the superior caval blood, but no holes in the segment lying in the right auricle. After insertion, the holes in the cannula are readily palpable through the caval wall, and their position in the venae cavae can be adjusted prior to securing the ligatures around the venae cavae and inclosed tubing. The upper end of the caval cannula was connected to the inflow tube of the pump.

The pump was started, and the caval venous return withdrawn through the cannula and pumped into the pulmonary artery. The vacuum and pressure in the pump were adjusted to empty the venae cavae of blood. The ligature previously placed around the superior vena cava was then securely tied around the polyethylene cannula just above the heart. The same procedure was followed for the ligature around the inferior vena cava just below the heart. The entire systemic venous return was thus made to pass through the caval cannula into the pump, none of it being permitted to reach the right side of the heart.

To remove the coronary venous return to the right heart a separate multiple-holed rubber or curved polyethylene cannula was inserted through a small incision in the tip of the right auricular appendage and directed into the right ventricle. The cannula was tied in position with the previously placed purse-string suture. In order to prevent escape of some of the coronary venous blood

into the pulmonary artery, and to prevent regurgitation of blood into the right ventricle from the pulmonary artery, the heavy silk ligature previously placed loosely around the base of the main pulmonary artery was tied securely before beginning the coronary flow measurements. This maneuver completed the isolation of the right side of the heart. In the absence of septal defects, of anomalies of venous return, or of leakage through the caval or main pulmonary arterial ligatures, the volume of blood then withdrawn from the cannula in the right auricle and ventricle is entirely of coronary sinus, cardiac venous, and thebesian venous origin—essentially the total coronary flow.

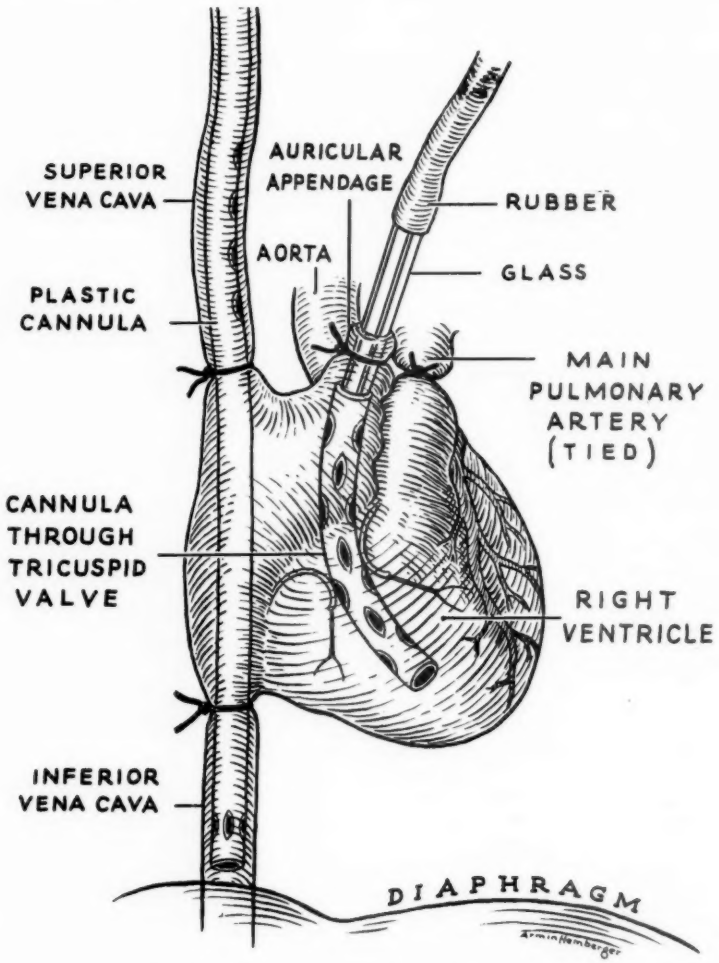

Fig. 2.—Diagrammatic sketch showing the cannulae for the removal of the caval and the coronary return.

This flow can be withdrawn and measured in a calibrated 50 c.c. burette, or it can be directed into an inverted Florence flask in which there is a fixed but controllable level of negative pressure (Fig. 3). When the coronary flow is directed into this flask through the higher (inlet) channel, it can then flow out through the lower (outlet) channel and into the pumping chamber where it

becomes mixed with the caval venous blood. When the coronary flow is selectively directed into the burette for measurement, the suction of the pumping chamber, which is finely balanced against the suction in the flask, will slowly withdraw blood from the reserve volume in the neck of the flask so that there is replacement of at least a portion of the blood flowing into the burette. Actually, the replacement is usually quite accurate as judged by the lack of change in the total flow or arterial blood pressure during measurement of the coronary flow. Occasionally, fluctuations in total flow readings, caused by spontaneous lowering or raising of the level of blood in the reservoir flask, make it virtually impossible to obtain a series of coronary flow readings under constant, unchanging conditions. The effect of an administered drug can also be masked by spontaneous changes of this kind. Experiments in which these variations were excessive have been eliminated from consideration.

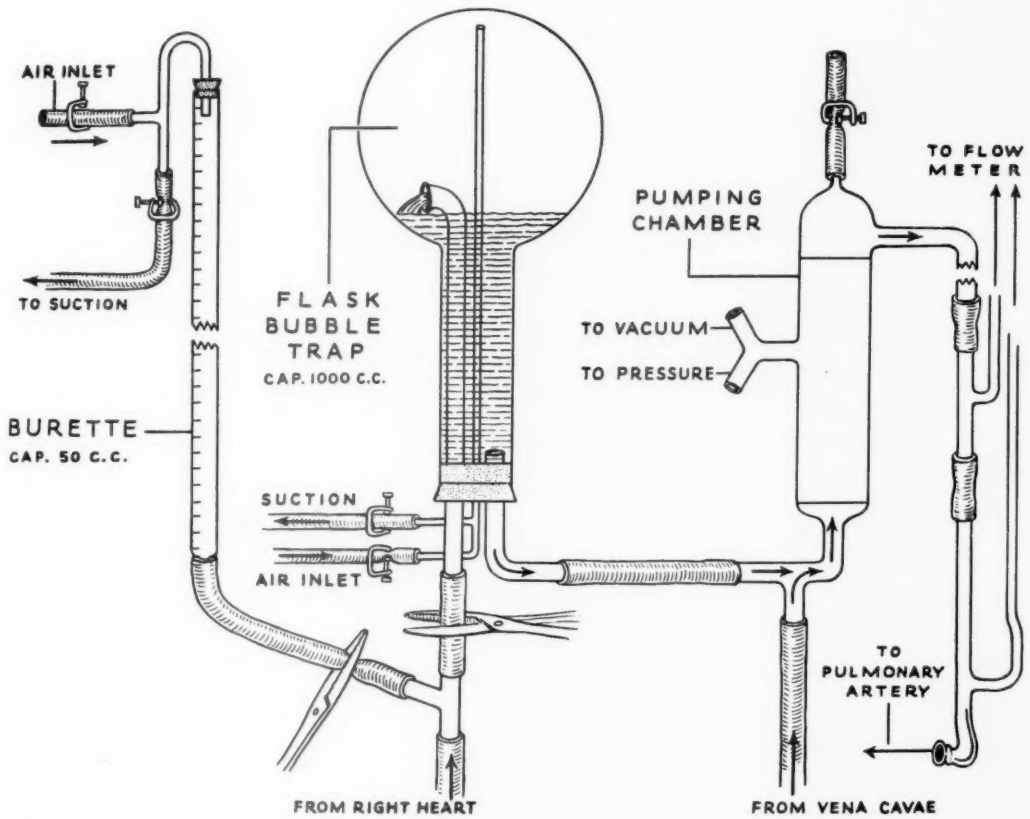

Fig. 3.—Diagrammatic sketch of the method used for the collection and measurement of the coronary venous return.

Technically this is a difficult experiment although, with practice, coronary flow studies can be started within an hour of the time the dissections are begun. Arterial hypotension is one of the most common complications encountered. In several experiments we have observed the development of an alarming, steadily progressive hypotension apparently unrelated to anesthesia, to blood loss, or to

TABLE I

EXP.	WEIGHT		ARTERIAL O_2	pH	CONSECUTIVE OBSERVATIONS		MEAN ARTERIAL B. P.		TOTAL BLOOD FLOW		CORONARY BLOOD FLOW			
	BODY (KG.)	HEART (GM.)	SATURATION (PER CENT)		NUMBER	TOTAL TIME (MIN.)	RANGE (MM. Hg)	AVERAGE	RANGE (C.C. PER MIN.)	AVERAGE	RANGE (C.C. PER MIN.)	AVERAGE	AVERAGE PER 100 GM. OF HEART	PER CENT OF TOTAL FLOW
1	14.6	120	99	7.19	8	11	12	111	82	1,392	5	55	46	3.9
3	19.7	197	92	7.01	8	9	8	122	63	1,935	10	130	66	6.7
4	12.8	95	100	7.13	8	11	12	101	138	1,256	8	42	44	3.3
5	10.3	89	100	7.13	8	7	14	105	104	1,102	11	49	49	4.4

trauma. On these occasions this effect was observed despite the fact that at the time the animal was receiving a transfusion of blood from another dog. The donor blood had been cross-matched with the recipient blood prior to administration and was found to be compatible. We were concerned by the failure of transfusion to elevate the blood pressure in these animals, and a more detailed study of the cross-matchings was made in subsequent experiments. Using trypsinized red cells in the cross-matchings to render the cells more sensitive to antigen-antibody reactions,[17-19] we found a very large number of incompatibilities, in marked contrast to cross-matchings made with nontrypsinized cells. Since making this observation, we have used only donors whose cells, when trypsinized, are compatible with the serum of the recipient and whose serum is compatible with the trypsinized cells of the recipient. Evidence to date, however, does not suggest that incompatibility as demonstrated by the trypsin technique is of major importance in causing transfusion reactions in the dog.

RESULTS

"Normal" Flows.—Coronary flows were studied and recorded in thirteen experiments in which post-mortem examination confirmed that occlusion of the superior and inferior venae cavae and of the main pulmonary artery was complete, and that there were no septal defects or obvious channels of anomalous venous return to the right side of the heart.

Four of the thirteen experiments were considered satisfactory for analysis of coronary flows. In all of these experiments the average mean arterial blood pressure was above 100 mm. Hg. The arterial oxygen saturation was above 90 per cent, and the total blood flows were within the normal range as reported by others.[10, 20]

Table I summarizes the findings in these four experiments. In each case the values given for coronary flow, total flow, and blood pressure are the averages of eight consecutive readings taken over a period of seven to eleven minutes. In all but one of these four experiments, these readings were the first eight consecutive determinations of coronary and caval flow that were made. In Experiment One, the first determinations of coronary and caval flow varied over a wide range due to technical difficulties, and the flows reported for this experiment were obtained after these difficulties had been corrected. The range of the average total coronary flows was from 42 to 130 c.c. per minute. When expressed in terms of cubic centimeters of blood per 100 Gm. of heart weight per minute the range is 44 to 66 c.c. When expressed in terms of per cent of cardiac output (total flow) the range is 3.3 to 6.7 per cent.

Anoxia.—In some of these experiments anoxia developed spontaneously, apparently coincidental with the onset of pulmonary edema of the perfused left lung. The effect of anoxia on coronary flow was always the same. As the oxygen saturation of the arterial blood fell, there was a progressive and marked increase in coronary flow. Changes in total flow and in arterial blood pressure were less consistent.

In Experiment One the effect of progressive anoxia was studied under well-controlled conditions. The coronary flow, the total flow, and the arterial blood pressure were observed and recorded for a long enough period of time to ascertain their stability. Arterial oxygen samples were drawn to be sure that the blood was fully saturated. The gas in the Rand-Wolfe respirator was then shifted from 100 per cent oxygen to a mixture containing approximately 10 per cent oxygen and 90 per cent nitrogen. This gas mixture was not immediately delivered to the lungs as the respirator bag and tubing were filled with oxygen

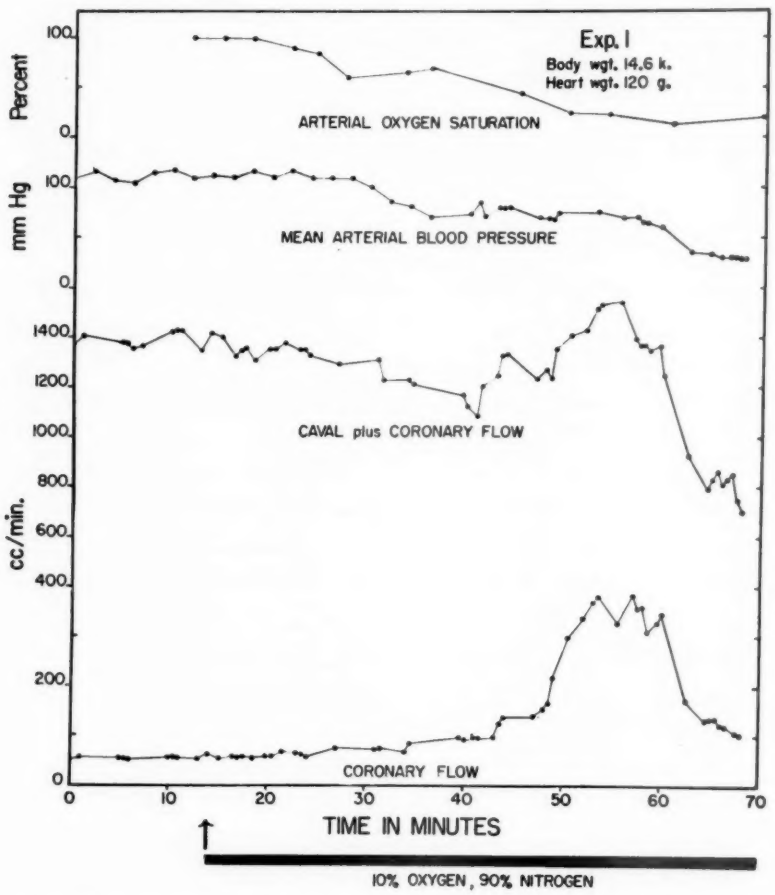

Fig. 4.—The effect of anoxia on the coronary flow, total flow, and arterial blood pressure.

at the time. The blood pressure, total flow, and coronary flow were observed at frequent intervals throughout the remainder of the experiment, and frequent determinations of the oxygen saturation of the arterial blood were made. As can be seen in Fig. 4, the total coronary flow showed a slight rise when the oxygen saturation fell below 90 per cent, and another slight rise when it fell below 85 per cent. With the oxygen saturation between 68 and 60 per cent there was a further slight rise. As the saturation fell below 60 per cent, there was a great increase in coronary flow which was maintained until shortly before the animal died. The average coronary flow during the control period was 55 c.c. per

minute. The highest flow recorded during severe anoxia was 381 c.c. per minute, a rise of over 690 per cent. During the control period the coronary flow constituted only 3.95 per cent of the total flow. When the coronary flow reached the maximum of 381 c.c. per minute, it then constituted 24.6 per cent of the total flow.

Adrenergic Drugs.—The effect of Neo-Synephrine Hydrochloride* on coronary flow was observed in many experiments. A few observations on the effect of Adrenalin Chloride and methoxamine hydrochloride were also made. The effect of these drugs on coronary flow appeared to be similar to that of Neo-Synephrine, but insufficient data are available for analysis.

Neo-Synephrine was administered in doses that invariably caused a rise in arterial blood pressure. The coronary flow rose in every experiment. The total flow occasionally rose slightly but usually remained unchanged, or fell, during the period of Neo-Synephrine effect. Fig. 5 shows a typical example of the effect of the intravenous administration of 75 c.c. of a 1:500 dilution of 1 per cent Neo-Synephrine in normal saline within a two-minute period of time. The coronary flow rose rapidly to a peak level of 269 c.c. per minute, representing a rise of 490 per cent above the control level, while the total flow showed little change. The mean arterial pressure also rose abruptly to 202 mm. Hg. Coronary flow, total flow, and blood pressure then all fell simultaneously. The coronary flow leveled out in essentially the same range as before the drug was administered. During the control period the coronary flow constituted 4.6 per cent of the total flow. At the peak of the Neo-Synephrine effect, the coronary flow had risen to 37 per cent of the total flow.

The largest coronary flows of all were obtained following the administration of Neo-Synephrine when the coronary flow was already elevated due to anoxia. In one experiment, in which the oxygen saturation of the arterial blood was between 40 and 50 per cent, the administration of 75 c.c. of a 1:500 dilution of 1 per cent Neo-Synephrine caused a rise in coronary flow from 230 to 700 c.c. per minute. At the peak of the coronary flow in this experiment, the total flow was only 1,325 c.c. per minute so that, by calculation, the phenomenal flow of almost 53 per cent of the cardiac output was found to be going through the coronary circulation.

Pitressin.—The effect of Pitressin† administered intravenously was studied in three experiments. In the dosages used, Pitressin caused a slight decrease in the dogs' coronary flow, no change or a slight decrease in the total flow, and a slight to moderate increase in the mean arterial blood pressure. Fig. 6 illustrates the results obtained in a typical experiment. One-half unit of Pitressin in 1 c.c. of saline solution administered intravenously caused a fall in coronary flow from 130 to 100 c.c. a 20 per cent decrease, followed by a gradual return to the original level in about 12 minutes. Twice the initial dosage of Pitressin was then administered, with the same effect. The terminal sharp rise in coronary flow was caused by the development of severe anoxia.

*Winthrop-Stearns, Inc., New York, N. Y.
†Parke, Davis & Co., Detroit, Mich.

DISCUSSION

The normal coronary flow in dogs under conditions simulating those which will exist during the performance of surgery on the open right heart ranges from 44 to 66 c.c. per minute per 100 Gm. of heart weight. This range is in accord with the values reported by Eckenhoff, Hafkenschiel, and Landmesser[10]

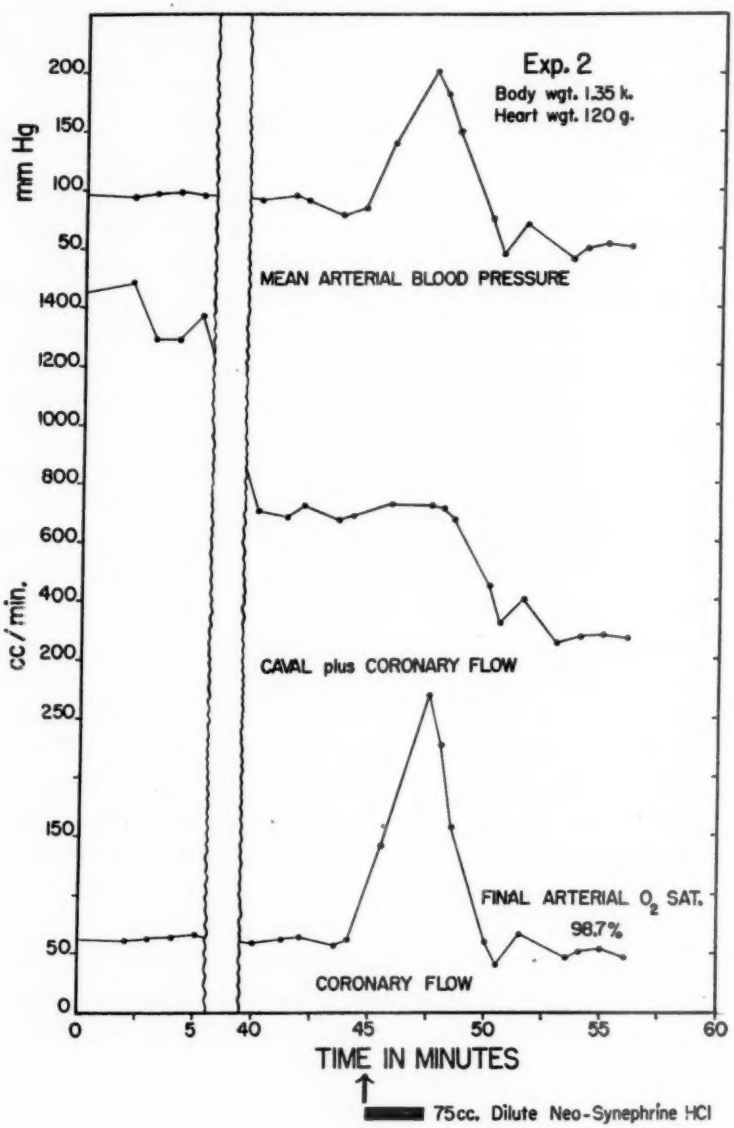

Fig. 5.—The effect of Neo-Synephrine Hydrochloride on the coronary flow, total flow, and arterial blood pressure.

for dogs breathing 100 per cent oxygen. It is slightly lower than the range reported by Gregg and co-workers[8] obtained by the nitrous-oxide and rotameter techniques. It is important to point out, however, that the flow values reported here represent flow per minute per 100 Gm. of *total* heart weight, whereas the

values reported in the literature represent flow per minute per 100 Gm. of left heart weight. Whether there is a significant difference between the two is uncertain at the present time.

Similarly, the values obtained for percentage of total flow going through the coronary circulation in these experiments are closely in keeping with those reported in the literature.[10]

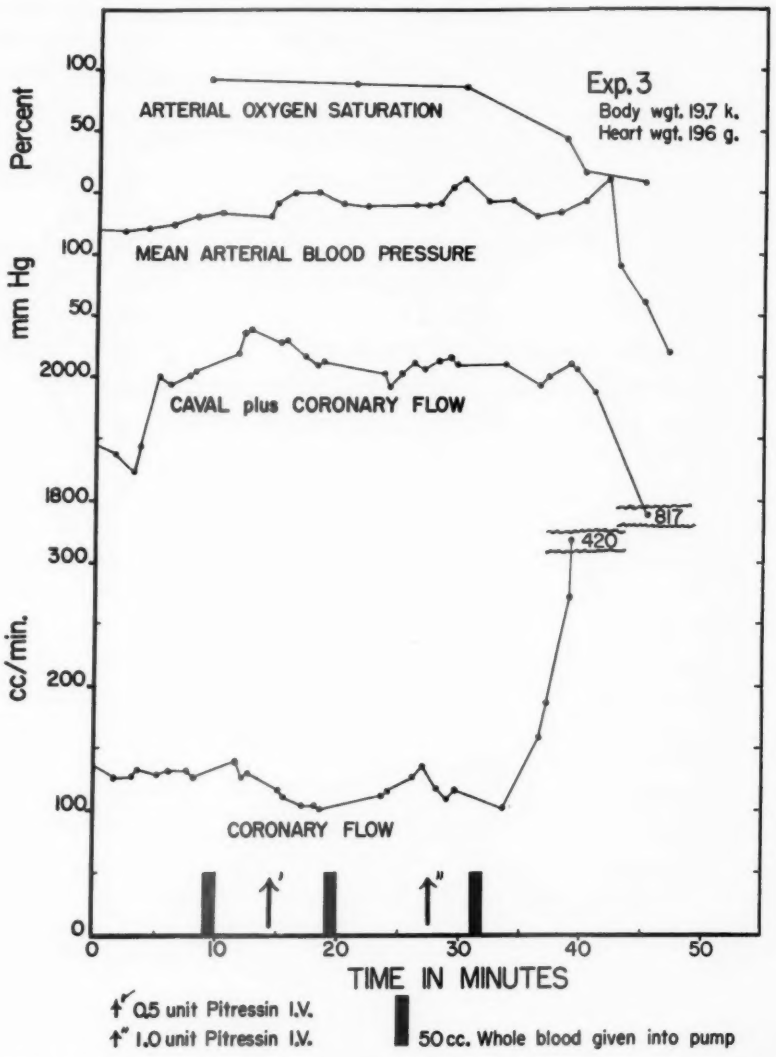

Fig. 6.—The effect of Pitressin on the coronary flow, total flow, and arterial blood pressure.

Hilton and Eichholtz[21] made the first detailed study of the effects of anoxia on the coronary blood flow in 1925, using heart-lung preparations. These workers found that the coronary vessels are extremely susceptible to anoxia. A fall of oxygen saturation below 20 per cent was found to cause maximal dilatation of the vessels with increases in flow up to 500 per cent. The findings in our experiments are similar to those of Hilton and Eichholtz. With severe anoxia, rises

in coronary flow to as high as 690 per cent of the control values were observed. The critical level of oxygen saturation of the arterial blood is not precisely clear. It seems that the major effect of anoxia on the coronary circulation takes place when the saturation falls to somewhere between 70 and 40 per cent. Above 70 per cent saturation there was actually little effect.

There is substantial evidence that epinephrine will cause an increase in coronary flow. Gregg[22] believes that this is due in part to a direct vasodilatation of the coronary vessels, but he states that it is difficult to separate the influence of a rise in aortic pressure. Eckenhoff and associates[10] have recently shown a direct vasodilatation of the coronary vessels with doses of epinephrine sufficiently small to cause an increase in neither blood pressure nor pulse rate. The dosages of Neo-Synephrine used in our experiments were always sufficiently large to result in an increase in aortic blood pressure. The occurrence of a great increase in coronary flow, usually with no significant rise in total flow, suggests that the increase in coronary flow was due in part to dilatation of the coronary vessels.

Several investigators have shown that Pitressin will cause a decrease in coronary flow due to coronary vasoconstriction.[22, 23] Our experiments confirm these observations although in none of these dogs was the coronary flow reduced more than 20 per cent. It would have been profitable to study the effect of the prolonged administration of Pitressin on the coronary flow.

These observations on coronary flow are important to the cardiac surgeon in several ways. It would appear that, at least with the right heart empty, a significant change in the normal flow through the coronary vessels is not to be expected. Should anoxia develop during the course of an operative procedure on the open heart, a significant increase in coronary flow will probably not occur until the oxygen saturation of the blood reaches a level of approximately 70 to 40 per cent. At about this level, however, there may be expected a sudden and very large increase in coronary flow. The removal from the open heart of this increased coronary flow, which might conceivably reach 1,000 c.c. per minute, would be extremely difficult, if not impossible. The increased coronary flow following the administration of adrenergic drugs would seem to contraindicate the use of these drugs in open heart surgery. From the few observations we have made on the influence of Pitressin on coronary flow, it does not appear that this drug will be of practical importance in decreasing coronary flow when this flow is excessive. However, further study of coronary vasoconstriction by this and other drugs, should be made.

Thus far we have confined our remarks to removal of the coronary venous return from the right side of the heart. The control of the coronary flow will be important to the surgeon operating upon the left side of the heart, even in the absence of septal defects. For, in addition to the thebesian flow directly into the cavities of the left heart,[14] if the coronary venous blood is not withdrawn from the right heart, the right ventricle will continue to pump it into the pulmonary artery, through the lungs, and then into the left auricle. Another problem which will confront the surgeon opening the left side of the heart is the return of bronchial venous blood, two-thirds of which drains through the

pulmonary veins and into the left auricle.[5] Under normal conditions this is not a large volume since the maximal total bronchial arterial flow draining into the pulmonary veins is 26.7 c.c. per minute in normal dogs.[20] However, in the presence of chronic lung disease[24] or the tetralogy of Fallot,[25] there may be an enormous increase in collateral bronchial arterial circulation and thus a great increase in the volume of bronchial venous return to the left auricle. This blood, like the coronary venous return, must be removed if operative procedures within the chambers of the heart are to be performed under visual control.

In view of the many problems which will arise with operations upon the open heart, it is probable that, for some time to come, closed intracardiac surgery will continue to be the method of choice. It is to be hoped, however, that eventually, with the aid of a unilateral heart pump or a complete heart-lung replacement, the heart can be opened with reasonable assurance of a successful outcome.

SUMMARY

In a series of experiments on dogs, the coronary and thebesian venous return to the right side of the heart was measured directly, with the caval venous return shunted past the right heart and into the pulmonary artery.

The normal coronary flow in dogs under these experimental conditions ranged from 44 to 66 c.c. per minute per 100 Gm. of total heart weight. Expressed in terms of per cent of total flow, the range was 3.3 to 6.7 per cent.

The effect of anoxia on coronary flow was always the same. As the oxygen saturation of the arterial blood fell, there was a progressive and marked increase in coronary flow. A rise in coronary flow of 690 per cent occurred in one experiment in which there was severe anoxia.

Neo-Synephrine Hydrochloride caused a great increase in coronary flow. However, in the dosages used there was invariably a rise in the mean arterial blood pressure.

Pitressin caused a diminution in coronary flow. With the dosages employed, the decrease was never greater than 20 per cent.

Further experiments on coronary flow are in progress, and will be reported in due course.

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MAINTENANCE OF LIFE BY HOMOLOGOUS LUNGS AND MECHANICAL CIRCULATION

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IN A previous communication[1] it was reported that adequate respiration in a dog can be maintained by directing some of the blood through homologous lungs. In these experiments the intact lungs were removed from a dog and connected with the circulation of an anesthized living animal. Blood from the aorta was directed to the pulmonary artery of the removed lungs and a connection between the pulmonary veins and the inferior vena cava of a living dog allowed the oxygenated blood to flow back into the circulation. No pumps were used. A tube was inserted into the trachea of the homologous lungs and to it was attached a soda lime canister, an oxygen tube, and an anesthetist's breathing bag. The living animal pumped part of its blood through the lung preparation where exchange of gases was accomplished by intermittent pressure on the breathing bag. A tracheotomy was done on the living animal and to the intratracheal tube was securely attached a small bag containing nitrogen. The animal could make respiratory movements but obviously could effect no exchange of gases in its own lungs. Animals were kept alive more than three hours while all "breathing" was done mechanically through homologous lungs.

It was concluded that exchange of gases, adequate to support life, can be accomplished by running part of the living dog's blood through the lungs of another animal of the same species.

The following group of experiments naturally followed. Guided by the fundamental work of Gibbon,[2] Jongbloed,[3] Björk,[4] Dennis,[5] Sirak,[6] Sewell,[7] and others on extracorporeal circulation and respiration we performed experiments similar to theirs except that we substituted homologous lungs for the mechanical gas exchange apparatus.

TECHNIQUE

Two dogs, one large, the other small, were chosen for each experiment. The dogs were routinely cross-matched, but no incompatibility of blood was found. The large dog was anesthetized with intravenous Nembutal, 1 c.c. of a 1 per cent solution for each 5 pounds of body weight. Five milligrams of heparin* for each kilogram of body weight were injected intravenously. The chest was widely opened by splitting the sternum longitudinally. As soon as air entered the chest the animal, of course, died. It is important when opening the chest to allow the animal to die before cutting the bone, to avoid air

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*The heparin solution was furnished by The Upjohn Company, Kalamazoo, Mich.

embolism. Two experiments failed because air was sucked into the circulation through the open veins in the cut surfaces of the sternum as the animal made agonal gasps.

The superior and inferior venae cavae, the azygos veins, and the aorta near its origin at the heart are doubly ligated and cut. If there is insufficient room to ligate the ascending aorta doubly, the large vessels of the arch may be ligated separately. The trachea is clamped and severed high and all attachments to the chest wall and esophagus are freed so that the heart and lungs may be removed en bloc.

The preparation is placed in a pan. The pulmonary artery is well isolated and a clamp is applied at the bifurcation. The pulmonary artery is severed as near the base of the heart as possible. The pulmonary veins are clamped and the heart is removed except for the left auricle. (It is easier to place one tube in the auricle than to cannulate all the pulmonary veins.) A de Pezzer catheter, with all but the flange removed, is placed in the left auricle and fixed with a snug purse-string suture. A glass tube, slightly flared to prevent its slipping out, is tied into the pulmonary artery. It is very important while inserting these tubes to leave the clamps on the pulmonary artery and veins so that air may not enter the circulatory system of the lungs. As a matter of fact, throughout these experiments one of the problems is to keep air out of the entire system.

A tube is inserted into the trachea and to it is attached a soda lime canister, an oxygen-carrying tube, and an anesthetist's breathing bag. The lung preparation is set aside and kept moist with saline solution. The large vessels in the chest of the dead dog are opened and all expressible blood is aspirated and placed in a pan for later use. It is quite essential to have plenty of blood in these experiments. Therefore, the large dog is chosen as the donor dog.

APPARATUS

The apparatus which serves as a mechanical heart has been made as simple as possible (Fig. 1. The picture tells more than a thousand words). It consists of two rotary pumps of the DeBakey type, one serving as the right ventricle, the other as the left ventricle. Two reservoirs, each a 1000 c.c. flask, serve as right and left auricles. In each flask is a three-hole rubber stopper into which glass tubes are snugly fitted. The flasks are held upside down so that there will be a longer column of blood to draw from when the apparatus is working.* The glass tube through which blood is drawn into the first flask, acting as the right auricle, extends halfway into the flask, and the glass tube on which suction is made extends well up into the flask. The third tube through which blood is drawn from the flask or reservoir extends just through the cork. The second flask which acts as the left auricle is similarly arranged.

These flask reservoirs serve as very essential safety factors since it is impossible to run both pumps at exactly the same speed. As the level of blood

*We are indebted to Dr. Clowes of Toronto, Ont., for this idea.

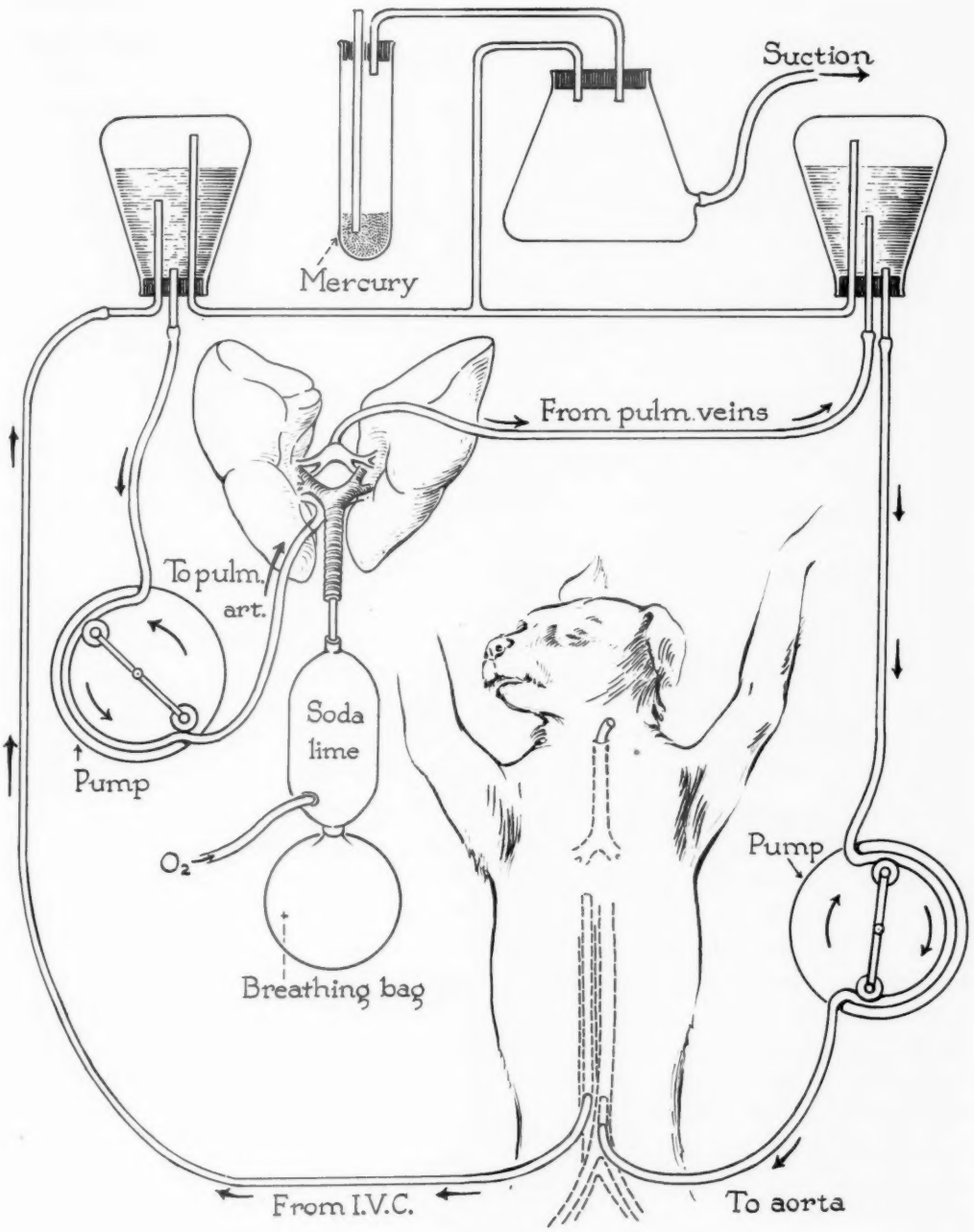
Suction
Mercury
From pulm. veins
To pulm. art.
Soda lime
Pump
O_2
Breathing bag
Pump
From I.V.C.
To aorta

Fig. 1.

rises in one flask, one pump is speeded up or the other is slowed down. Without these reservoirs, air is easily sucked into the system and if pumped into the living animal promptly causes death by occluding the coronary arteries. Furthermore, if air should be drawn into the system as blood is drawn from the inferior vena cava or from the lung preparation this air is trapped in the flask.

A simple system for negative pressure is attached to both flasks. In order that negative pressure may not be excessive a column of mercury 15 mm. high is inserted as a safety factor in the suction line. We depend upon continuous suction to draw the blood from the inferior vena cava into the flask serving as the right auricle and from the pulmonary veins of the lung preparation into the flask serving as the left auricle. This negative pressure of 15 mm. Hg approximates the negative intrathoracic pressure and prevents collapse and occlusion of the inferior vena cava and pulmonary veins. The first pump serves only to force blood into the lung preparation, the second to force blood into the aorta of the living animal.

PROCEDURE

The smaller dog is now anesthetized with Nembutal, morphine, and atropine. A tracheotomy is done so that respiration may be easily taken over during or at the close of the experiment. The abdomen is opened through a low right rectus incision; the aorta and inferior vena cava are exposed just above the level of bifurcation. At this point 5 mg. of heparin per kilogram of body weight are injected into the inferior vena cava. The aorta is ligated at the bifurcation and a plastic tube of proper size is inserted approximately 2 cm. and tied in place. The inferior vena cava is likewise ligated. A long plastic tube with many holes in the distal 8 inches, and of smaller caliber than the vessel, is rapidly inserted upward to the level of the superior vena cava.

While this procedure is being carried out by one worker, others are preparing and connecting the pumps, reservoirs, and lungs. The entire system and all connections are filled with physiologic salt solution and completely freed of air. Some of the salt solution is pumped out and replaced by heparinized blood. The tube leading from the inferior vena cava goes to the first reservoir which is connected to the pump serving as the right ventricle. This pump forces the blood into the lung preparation through the pulmonary artery. The tube in the left auricle of the lung preparation goes to the second reservoir connected with the second pump which acts as the left ventricle and forces the blood into the aorta of the living animal.

All tubes are, of course, clamped as preparations are being completed. As the final connections are being made the open ends of the tubes are carefully filled with saline solution or blood to eliminate all air. A glass T tube with a rubber tube attached to the long arm is inserted somewhere in the system to facilitate the addition of blood as necessary.

The clamps are now removed and the pumps set in motion. Respiration in the lung preparation is begun immediately by making quick intermittent

pressure on the breathing bag. The elasticity of the lungs is sufficient to collapse them as pressure is released and allow for to-and-fro absorption of carbon dioxide in the soda lime canister.

When all is going well the dog's chest is widely opened transversely to allow observation of the heart and occlusion of the inflow tract at the right auricle.

DISCUSSION

All of these experiments have been acute with no attempt at sterile technique or animal recovery. In this group of experiments, dogs were kept alive one and one-half hours "breathing" entirely with homologous lungs and for one-half hour with the inflow tract to their hearts shut off. The right auricle has been opened to establish the fact that no blood but that from the coronaries was flowing through the heart. Since it had been established in previous experiments that a dog could survive and again take over his own respiration after three hours of breathing by homologous lungs, it was our aim in these experiments to establish that extracorporeal circulation can be accomplished with pumps while using such lungs, and that life will continue while blood flow through the animal's heart is completely stopped. Although successful experiments have been performed without too much trouble by a team of three or four workers, there are a number of small details which in a moment can result in failure. The greatest hazard is the admission of air into the system. It is well known that a considerable amount of air will do little damage if it goes into the lesser circulation but if tiny quantities of air get into that part of the system which is pumping blood into the aorta the bubbles seem to find their way promptly to the coronary arteries. At that point the experiment is over.

It is essential to have the plastic tube in the inferior vena cava smaller than the vessel so that blood from the renal veins and gastrointestinal system can be aspirated. One experiment failed because the tube in the inferior vena cava was approximately the size of the vessel. When suction was made the wall of the vessel was sucked into the holes in the tube and little blood could be aspirated.

"Breathing" in the homologous lungs, we have found, should be done by rather rapid (about 50 per minute), intermittent, and not too vigorous pressures on the breathing bag. Occasionally bloody froth has accummulated in the tracheobronchial system of these lungs. Whether this was due to too-vigorous pressure on the breathing bag or to too-high pressure in the pulmonary artery we do not know. Pulmonary edema sometimes occurs, also for causes unknown. If the edema is not too severe, the tracheal tube may be removed and the lungs aspirated without interference with function. Twice we removed the lungs from a heparinized dog and kept them in the icebox overnight. When they were attached to the living dog the following morning severe pulmonary edema developed promptly and the dog died.

In one instance the animal was not deeply enough anesthetized to lie perfectly still. Administration of a small amount of ether in the intratracheal

tube of the lung preparation produced satisfactory anesthesia. It would be expected that since oxygen is absorbed and carbon dioxide is given off, that ether also would be absorbed.

We have made the mistake of giving the dog from which the lungs were to be taken enough Nembutal for complete anesthesia. We then took all the blood from the dead animal without realizing that it contained much Nembutal. When this blood was given as a transfusion to the living animal anesthesia, of course, was too deep. No wonder it took a long time for the dog to wake up. Undoubtedly the fact that many dogs went into apnea shortly after the experiment was begun was due to excessive Nembutal.

It is inappropriate to hasten to any conclusions on the basis of this work. Much remains to be done, although blood studies have confirmed what is apparent to the naked eye—cyanotic blood going to the lung preparation and pink blood coming from it. A detailed study remains to be done of the oxygen and carbon dioxide content and of the pH of the blood after hours of "breathing." Gas analyses of air in the lung preparation are in order.

A natural question is this—will heterologous lungs likewise be effective? This subject is under investigation.

CONCLUSIONS

It has been demonstrated that exchange of gases adequate to sustain life can be accomplished by pumping all the blood of a dog through homologous lungs. It has also been demonstrated that the heart may be opened while employing this method of extracorporeal respiration.

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